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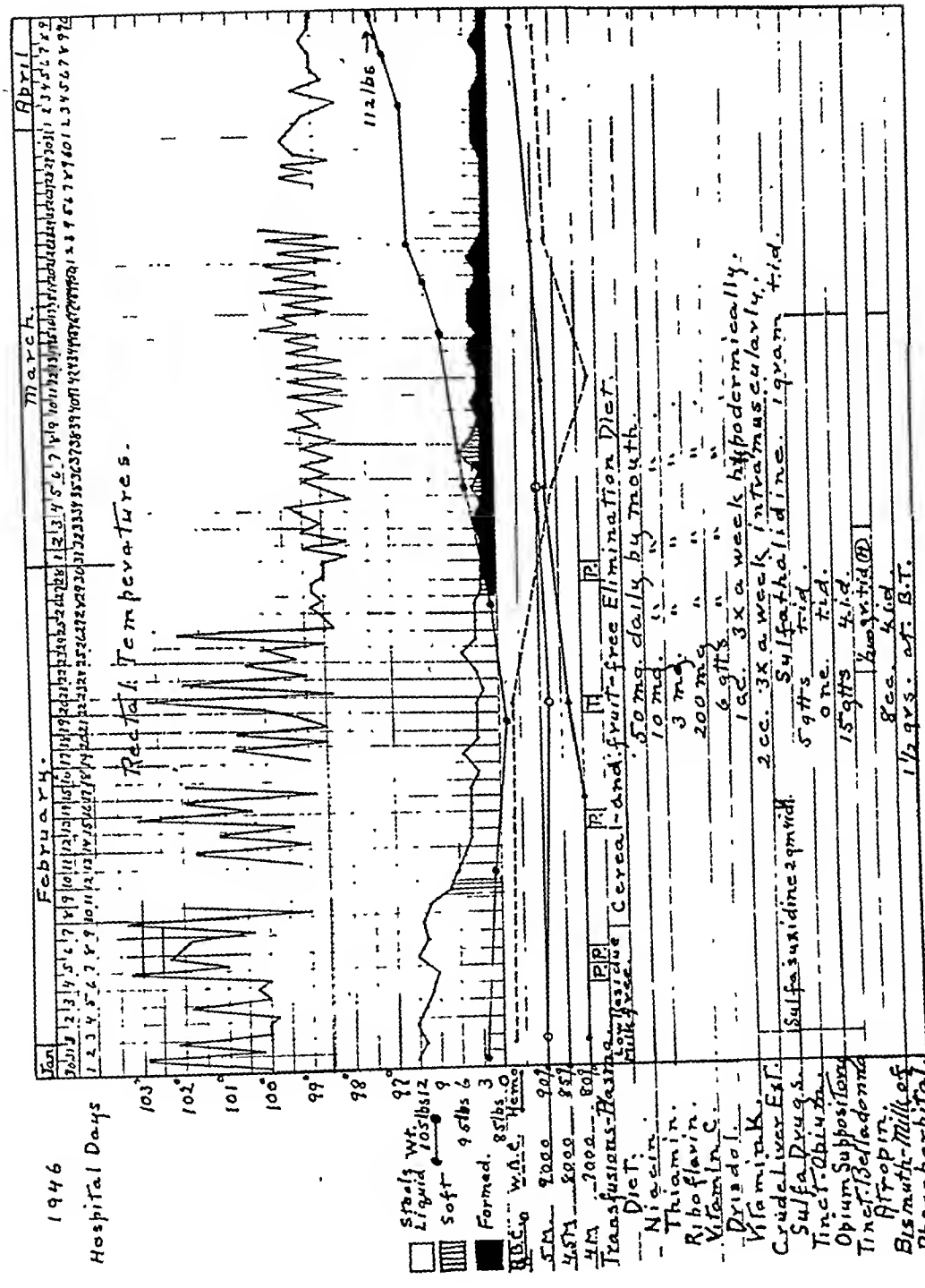

Fig. 4. *Case 5.* Mrs. R. G., aged thirty. This fulminating chronic ulcerative colitis was controlled with the fruit and cereal-free elimination diet. The benefit from the sulfonamides and the small dose of crude liver extract is uncertain. The necessity of all the sedatives and antispasmodics is questioned today. The steady gain in weight after the diarrhea and fever were reduced occurred with no change in the diet, and with no milk, egg or other common allergenic foods in the diet. The excellent control of this colitis in the last three years had depended on strict adherence to the diet and in the last one and one-half years on the control of pollen allergy, which is of probable secondary importance to this major food allergy.

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—report 3 independent investigators

The theory that an allergic reaction is the trigger mechanism in the common cold is gaining wide acceptance. Three reports have been published by independent investigators on their use of Pyribenzamine to abort the common cold. All stress that treatment begun within a few hours after onset of symptoms produces the greatest benefits.

★

Results of Treatment of Common Cold with Pyribenzamine

Persons treated	Number	Benefited	%
Students[1]	252	224	89
Factory Workers[2]	494	397	80
Naval Personnel[3]	466*	348	75

*Includes patients treated with other antihistaminics.

1. Gordon, John S.: Laryngoscope, 58: 1265 (Dec.) 1948.
2. Murray, H. C.: Indust. Med. 18: 215 (May) 1949.
3. Brewster, John M.: U. S. Nav. M. Bull. 19:1 (Jan.-Feb.) 1949.

Pyribenzamine Expectorant—Each teaspoonful contains 30 mg. Pyribenzamine citrate, 10 mg. of ephedrine sulfate and 80 mg. of ammonium chloride.

Dosage—Adults: 1 or 2 teaspoonfuls every 3 to 4 hours followed by a small glass of water.
Children: ½ to 1 teaspoonful every 3 to 4 hours.

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Dosage—1 application to each nostril every 3 to 4 hours.

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1. Horton, B.T., Ryan, R. E. & Reynolds, J. L., Proc. Staff Meet. Mayo Clinic, 23.105, Mar. 3, 1948.
2. Friedman, A. P., N. Y. State Jl of Med. (in press).
3. Ryan, R. E., Postgraduate Medicine (in press).
4. Hansel, F. K., Annals of Allergy (in press).

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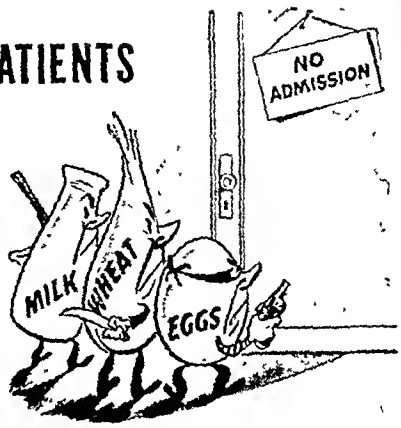

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TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 1 (Davies)																
Alternaria	+			++++	++++	−	+++	+++	+++	++	+++	+	+++	+	+	+++
Hormodendrum	+			++++	++++	−	++	−	+++	+	+++	−	+++	−	+	++
Helminthosporium	+			+++	++++	+	++	+++	+++	−	+++	+	+++	−	++	+++
Spondylocladium	++			++++	+++	+	++	+++	+++	−	+++	−	+++	−	++	+++
Curvularia	++			++++	++++	−	++	+	+++	+	+++	−	+++	−	++	++
Nigrospora	−			−	+++	−	++	−	+++	++	+++	−	+++	−	+	−
Control					+++		++		+++		+++		+++		+	
Patient 2 (Rowles)																
Alternaria	+	++	+++		++++	−	+++	++++	++	+++	++	++++	+	++++	++	++++
Hormodendrum	+	+	+++		++++	−	++++	−	++	+	++	++	++	++	++	−
Helminthosporium	−	+	++		++++	−	+++	−	+	−	++	−	++	+	+++	−
Spondylocladium	+	+	++		++++	−	+++	−	++	−	+++	−	+++	−	++	−
Curvularia	++	+	++		++++	−	+++	−	+++	−	++	−	++	−	+++	−
Nigrospora	−	−	−	+	++++	−	+++	−	+++	−	++	−	++	−	++	−
Control					++++		++		++		+		+		++	
Patient 3 (Keene)																
Alternaria	++		++		++++	−	++	++++	+++	+	++++	+	++	−	++	++
Hormodendrum	++		+		+++	−	++	−	+++	−	+++	−	+++	−	++	++
Helminthosporium	++		++		+++	++	++	+++	+++	−	+++	−	+++	−	+++	+++
Spondylocladium	+++		++++		+++	+++	++	+++	+++	+	+++	−	+++	−	+++	+++
Curvularia	−		++		+++	+++	++	+++	+++	+	+++	−	+++	−	++	++
Nigrospora	+		+		+++	−	++	−	+++	+++	+++	−	+++	+	+++	−
Control					++++		++		+++		++++		+++		+++	
Patient 4 (Hornbuckle)																
Alternaria	++		+++		++++	−	−	+++	+++	++++	++	++++	++	+++	−	++++
Hormodendrum	−		−		++++	−	+	−	++	−	++	−	++	−	−	−
Helminthosporium	+++		++		++++	−	−	+	++	−	++	−	++	−	−	++
Spondylocladium	++		+		++++	−	−	+	++	+	++	−	++	−	−	++
Curvularia	+		++		++++	−	+	−	+	−	++	−	+	−	−	+
Nigrospora	−		−		++++	−	+	−	++	−	++	−	+	−	−	−
Control					++++		−		++		+++		++		−	

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TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 9 (Bruggeman)																
Alternaria	++++	+	++++		++++	−	++++	++++	+++	++++	++++	++++	+++	++++	+++	++++
Hormodendrum	++	+++	+++		++++	−	++++	−	+++	+	++++	−	++++	−	+++	−
Helminthosporium	+	−	++		++++	−	++++	−	+++	−	++++	−	+++	−	+++	++
Spondylocladium	++++	++	++++		++++	−	++++	+++	+++	++++	++++	−	++++	+++	+++	+++
Curvularia	+++	+	++++		++++	−	++++	−	+++	−	++++	−	+++	−	+++	+++
Nigrospora	−	−	+		++++	−	++++	−	+++	−	++++	−	++++	−	+++	−
Control					++++		+++		++		++++		+++		+	
All neutralizations carried out spontaneously.																
Patient 10 (Hansen)																
Alternaria	+			+++	++++	−		++++		++++		++++		++++		++++
Hormodendrum	−			−	++++	−	−									
Helminthosporium	−			−	+++	−			−							
Spondylocladium	−			−	++++	−					−					
Curvularia	−			−	++++	−							−			
Nigrospora	−			−	++++	−									−	
Control					++++											
Note: This patient obviously sensitive only to Alternaria. No other molds reacted, and sites later tested with Alternaria all reacted. Recipient refused further participation.																
Patient 11 (McMinn)																
Alternaria	+			++	+++	−	−	+++	+++	+++	++	+++	+++	+++	−	+++
Hormodendrum	−			−	+++	−	−	−	+++	−	+++	−	+++	−	−	−
Helminthosporium	−			++	++	−	−	+++	+++	−	+++	+++	++	+++	−	+++
Spondylocladium	+			++	+++	−	−	++	+++	−	++	−	++	+++	−	++
Curvularia	−			+	+++	−	−	++	+++	−	++	−	+	−	−	+
Nigrospora	−			−	+++	−	−	−	+++	−	++	−	++	+	+	−
Control					+++		−		++		+++		++		++	
Patient 12 (Hixon)																
Alternaria	++++		+++		++++	−	+	++++	−	+++	+	++++	+	+++	+++	++
Hormodendrum	−		+		++++	−	++	−	+	++	++	−	−	++	++	+
Helminthosporium	−		−		++++	−	+	+	+	−	++	−	−	++	++	−
Spondylocladium	−		+		++++	−	+	−	++	++	++	−	−	++	++	−
Curvularia	−		−		++++	−	++	−	++	++	++	−	−	−	+++	−
Nigrospora	−		−		++++	−	+	−	−	−	++	+	−	++	++	−
Control					+++		+		−		++		−		++	

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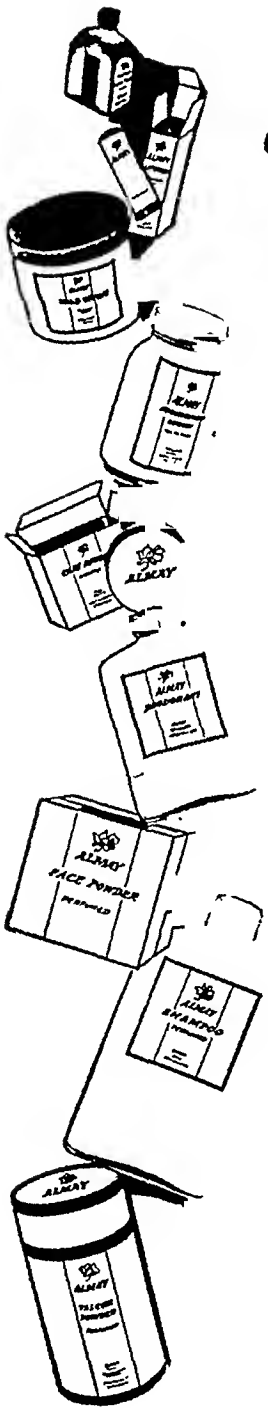
TABLE II. IN-VITRO NEUTRALIZATION TESTS

Serum—Saline—Antigen:	Alternaria		Hormodendrum		Helminthosporium		Spondylocladium		Curvularia		Nigrospora	
Cross testing with:	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000
Patient 1 (Davies)												
Alternaria	−	−	+++	−	+	−	+	−	++	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	+	−
Helminthosporium	++	−	++++	−	−	−	+	−	+	−	+++	−
Spondylocladium	−	−	++	−	−	−	−	−	−	−	++	−
Curvularia	−	−	++	−	−	−	−	−	−	−	+	−
Nigrospora	−	−	−	−	−	−	−	−	−	−	−	−
Control A 1/3 serum	+	−	+	+++	+++	−	+++	−	++	−	−	−
Control B serum undiluted	+++	−	++	+++	+++	−	+++	−	+++	−	+	−
Patient 2 (Rowles)												
Alternaria	−	−	++++	−	++++	−	++++	−	++++	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	−	−
Helminthosporium	−	−	−	−	−	−	−	−	−	−	−	−
Spondylocladium	−	−	−	−	−	−	−	−	−	−	−	−
Curvularia	−	−	−	−	−	−	−	−	−	−	−	−
Nigrospora	−	−	−	−	−	−	−	−	−	−	−	−
Control A 1/3 serum	++++	−	++	++	+++	−	−	−	−	−	++	−
Control B serum undiluted	+++	−	++	+++	+++	−	+++	−	+	−	+++	−
Patient 3 (Keene)												
Alternaria	−	−	++++	+	+	−	++	−	+	−	+++	−
Hormodendrum	−	−	−	−	−	−	−	−	−	−	−	−
Helminthosporium	++	−	+++	−	−	−	−	−	−	−	+++	−
Spondylocladium	+++	−	++++	−	++	+	−	−	−	−	++++	−
Curvularia	++	+	+++	+	+++	+	++	−	−	−	+++	−
Nigrospora	−	−	−	−	++	++	+++	−	−	−	−	−
Control A 1/3 serum	+++		+	+	++	+	+++		+++		+	
Control B serum undiluted	+++		++	+	+++	++	+++		+++		++	

Allergic people

can also use fine cosmetics



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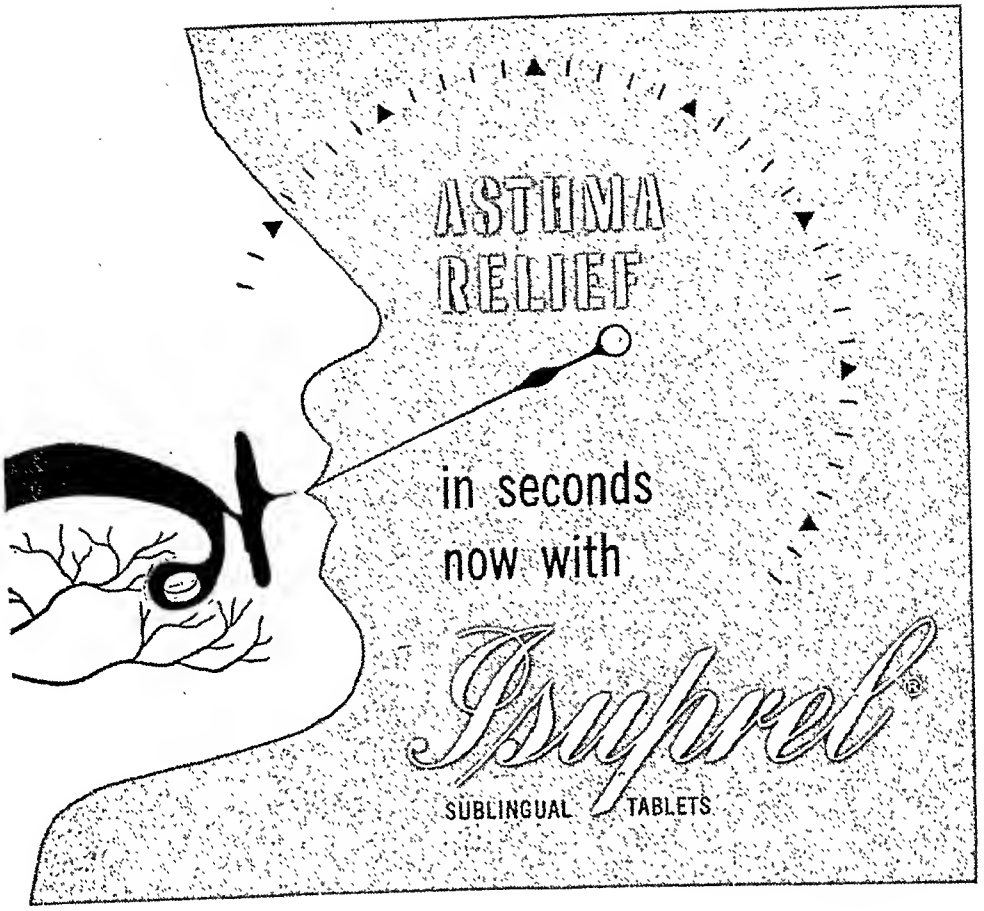

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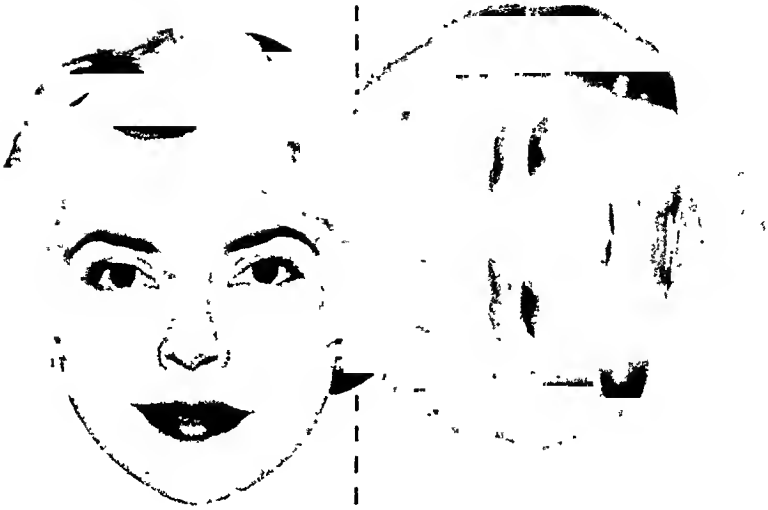

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Magnitude of dosage was largely a matter of arbitrary opinion on our part. It ranged from three to six or even eight 2-ounce doses daily. The total potency from three 2-ounce "cocktails" in terms of individual significant ingredients may be stated as follows:

Available Amino Acids	42 Gm.
B_1	8.4 mg. (8.4 x M.D.R.)
B_2	15.0 mg. (7.5 x M.D.R.)
Niacin plus niacinamide	120.0 mg.
Vitamin A	18,000 U.S.P. units (4.7 x M.D.R.)
Vitamin D	1,500 U.S.P. units (3.7 x M.D.R.)
Vitamin C	90.0 mg. (3 x M.D.R.)

plus rich quantities of the natural vitamin B complex as described.

We feel that because the interrelationship among all these nutritional factors has been unquestionably established, it is important in attempting management of the patient in nutritional failure, whether of allergic etiology or not, to include all features—not just amino acids or vitamins. The "basic three," as described, is ideal for our purposes. It contains, in the light of present understanding, all nutritional units, in easily assimilable form, necessary for quick tissue construction and repair and also for the necessary boosting of deficient detoxication and antihistaminic mechanisms undoubtedly prevalent in allergic states. Furthermore, we can theorize that this nutritional formula is especially advantageous in allergic states because of the relatively nonantigenic character of its protein content, allowing the patient to establish generous nitrogen balance in spite of apparent intolerance to many protein foods.

Therapy with this nutritional schedule has shown great promise. For about two years, we have employed this approach in eczema and bronchial asthma of allergic origin and can point to exceptionally fine results, by and large. At this time we are presenting four typical case histories where the therapeutic nutritional program was instituted and followed through as the sole measure of treatment.

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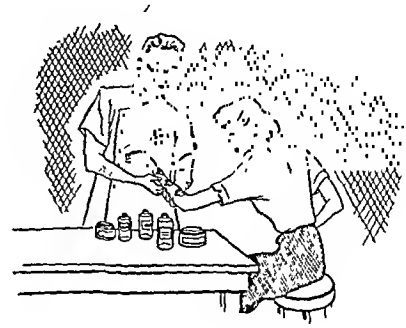
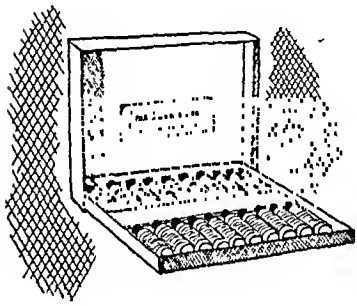
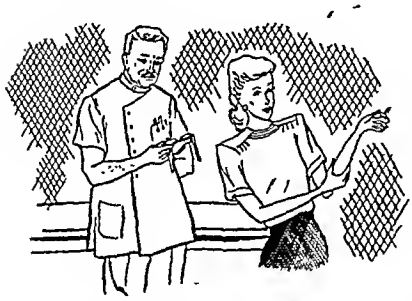




2) Secondary tests with constituents of products causing reaction, to trace offending agents. (In specific cases, on written request, we supply testing materials, gratis.)

3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)



4) Final check tests with modified formulae to make certain there is no reaction.

Preparations by Luzier are regularly available in an unscented variation. They do not contain orris root or rice starch. Any of their normally harmless constituents, however, is potentially allergenic, for which reason we suggest testing, when practicable. Fees for such tests are patient's responsibility.

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ointments. The eczema progressed to the state where it covered the entire body and was especially severe at the folds of the skin. Eight months ago, we started the nutritional formula in large amounts (six to eight doses daily). Improvement was noted very shortly and was marked after three months. The itching subsided and the patient was enabled to sleep comfortably almost immediately after treatment was instituted. The skin cleared over the broad surfaces. In eight months the entire skin had healed, leaving only thickened areas at the folds of elbows, knees and thighs. The patient gained 30 pounds. She has been on a full diet for the past eight months. She has eaten foods which at one time would have immediately precipitated an asthmatic attack.

SUMMARY AND CONCLUSIONS

1. In commenting on these cases, it is of interest to note that establishing the patient on optimal nutrition with the "basic three" formula not only resulted in relief, healing and apparent cure of the allergic syndrome, but also enabled the individual in each instance to tolerate foods and other allergenic agents to which he had been sensitized prior to treatment.

2. This can only be described as a preliminary study. We are employing the nutritional approach generally; however, in the majority of cases the patients have not appeared for final check-ups, thus preventing us from submitting a greater number of histories. About twenty-five patients are under treatment at the present time, and considerable effort is being spent in recording complete periodic data. These histories will be submitted in a future presentation.

3. From our results and observations up to the present time, dealing with the allergic state resolves itself chiefly into a metabolic study. The problem may be attacked with a promising degree of success by the application of therapeutic nutrition, which includes a biologically potent protein hydrolysate, the complete vitamin B complex mainly from mixed natural sources, and therapeutic quantities of all other vitamins, incorporated in one formula in balanced proportion.

We will not presume to offer adequate theories of the biologic processes involved which might explain the improvement noted in these patients; this problem is far too involved in the light of present limited knowledge to justify completely our beliefs. However, by supplying the patient with nutritional factors, as described, in easily assimilable form, it is conceivable that the antigenic process may be arrested and even reversed. This may be brought about by (a) cell alteration in shock tissue, (b) an increase of pancreatic enzymes in the blood serum and digestive tract, and (c) a stimulation of detoxication, antihistaminic and antibody mechanisms essential to combat successfully the degenerative process in allergic states.

4. The formula used in treatment probably does not represent complete nutrition in the absolute sense. We believe that carbohydrate may be omitted in terms of its possible place in the therapeutic nutritional scheme. However, fat metabolism may be important, especially the essential unsaturated fats. Hansen[1] has found that many eczematous patients dis-

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OBSERVATIONS ON SEVERE PENICILLIN REACTIONS

M. H. SAMITZ, M.D., and PETER N. HORVATH, M.D.
Philadelphia, Pennsylvania

THERE are numerous reports in the literature describing generalized cutaneous reactions to penicillin.[1,3-7] These reactions vary from mild urticaria to severe exfoliative dermatitis. Skin testing has been done in most of these cases to demonstrate conclusively penicillin sensitivity, and penicillin sensitivity has been experimentally induced.[2,8] We are reporting two cases of generalized cutaneous reactions to penicillin and their clinical courses.

CASE REPORTS

Case 1.—J. C., colored man, forty years old, gave a history of a penile sore ten years ago, for which he received numerous arm and hip injections over a period of five years. He had had a recurrent, pruritic, oozing eruption involving the penis, scrotum and crural areas for the past five years. This eruption recurred in May, 1946, and the patient was treated by his family physician, who put him on a salt-free diet, administered injections of Hapamine and gave auto-hemotherapy, to no avail. In September, 1946, the patient received two injections of penicillin (in beeswax) four days apart, and four days after the second injection a generalized eruption appeared.

On admission, he presented a generalized eczematous eruption, with lichenification and excoriation marks, most prominent in the intertriginous areas. The only other unusual finding was a generalized lymphadenopathy. The hospitalization period lasted thirty days, during which time he received a variety of medicaments, including starch baths, sedation, Pusey's oil emulsion to the skin, and nicotinic acid amide intravenously. There was a slight flare-up following administration of barbiturates. While the eruption was undergoing resolution, a patch test was performed using sodium penicillin in distilled water (50,000 units per c.c. of solution). There was no reaction to this patch test, but within forty-eight hours an acute flare-up, consisting of vesicles and oozing, developed at the site of previous lesions. There also was moderate edema of the face and extremities and severe pruritus.

The patient's condition gradually subsided, and he was discharged in moderately good condition. Since then, he was seen only occasionally, but he still had pruritus and lichenification, with occasional oozing at previous sites of involvement.

Case 2.—H. M., twenty-nine-year-old colored woman, gave a history of having had virus pneumonia in 1945. She was given penicillin tablets at this time, and within twelve hours after ingestion of the penicillin developed nausea, vomiting and weakness. In March, 1947, following the application of a hair straightener to the scalp, she developed a folliculo-pustular eruption of the scalp. She was again given penicillin tablets, and within twelve hours developed a generalized exudative, eczematous eruption, most prominent on face, neck, scalp and the intertriginous areas.

She was treated on an out-patient basis for two months, and she was found to be sensitive to aquaphor and olive oil. She did not improve, so she was hospitalized. She received starch baths, Benadryl, and various topical bactericidal agents, and improved slowly. She reacted repeatedly to the administration of paraldehyde with

Dr. Samitz is chief of Dermatology Clinic, Graduate Hospital; Assistant professor of dermatology, Graduate School of Medicine, University of Pennsylvania. Dr. Horvath is a fellow in dermatology, University of Pennsylvania.

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kindly supplied by the Chief Forest Products Officer of the Department of Forestry of the Union of South Africa.

1. Congo hardwood: There is no recognized botanical or scientific name. The term probably includes a group of rather similar woods.

2. Western Red Cedar, *Thuja plicata*: This is the well-known shingle wood imported from America. It is a soft, light, fairly durable reddish-brown timber.

3. Kejaat (Kiaat), *Pterocarpus angolensis*: One of the best local timbers for furniture and all high class joinery work. An attractive brown, very durable wood. Grows in the North and North Eastern Transvaal, but most of the wood used in the Union is imported from Portuguese East Africa.

4. Mvuli (Iroko), *Chlorophora excelsa*: One of the best known African timbers. A brown wood with properties and uses similar to kejaat. Not grown in the Union but scattered throughout the greater part of East and West Central Africa.

5. Partridge: Most probably Panga-panga, *Millettia stuhlmanii*. A brownish black wood with a strong figure. Rather heavier than teak and used for sleepers and furniture. All supplies imported from Portuguese East Africa.

The patient himself suspected the wood dust in the factory as a cause of his troubles because his chest became constricted after a few minutes of inhaling wood dust while at work.

During the course of the day he was troubled with continuous sneezing, running of the nose and wheezing. On returning home in the evening he felt too ill to eat. He usually cycled to and from his place of employment, but an attack of asthma always accompanied this exertion. Asthmatic attacks occurred every night, with loss of sleep and exhaustion and an adverse effect on his general health.

The factory was closed on Saturdays and Sundays, and on these nights the patient remained free from asthma. After a time he was only able to work from Monday to Wednesday, as the increasing severity of the asthma attacks rendered him unfit to continue with his work for the remainder of the week.

Skin tests were carried out on the patient with a large variety of inhalant substances including local pollens, animal danders, house dust, feathers, kapok, orris root, et cetera, all with negative results. Skin sensitivity to foods was not especially tested for. The patient had no food idiosyncracies, but certain foods, including paw-paw, produced vomiting if taken after an attack of asthma. Although skin sensitivity to feathers was not elicited, he was advised to remove feathers from his home, but the nightly attacks of asthma still continued. For a period of two months the patient had lived in a house where the walls were rather damp, and the possibility of mould sensitivity was considered. Skin tests with a variety of airborne fungus extracts produced negative reactions. Extracts were prepared from moulds collected by plate exposure in his own house. Skin tests done with these extracts gave negative reactions. The patient moved to another house but there was no cessation in the attacks of asthma.

Extracts of the same weight-volume concentration were prepared in buffered saline solution from the woods which the patient customarily handled. The following are the results of the skin tests carried out with these extracts:

Wood	Reactions to: Scratch Test	Intradermal Test
Kejaat	Very strong (+++)	Not done
Congo hardwood	Moderate (++)	strong (+++)
Western red cedar	Moderate (++)	Moderate (++)
Mvuli	Trace (±)	Slight (+)
Partridge	Trace (±)	Slight (+)

It will be observed that the patient showed marked skin reactions to kejaat and Congo hardwood and was moderately sensitive to Western red cedar.

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By May, 1947, the patient was receiving 0.1 c.c. of a full strength extract intradermally, a dose which produced a wheal of about half an inch in diameter with pseudopodia and which was continued subsequently at monthly intervals for a period.

By December, 1947, the patient had been free from all allergic symptoms for about a year although no change had occurred in the working conditions.

In that month the factory closed down and the patient found occupation in another factory, where he worked for only three weeks because he began to sneeze and cough and suffered one relatively mild attack of asthma. He left because he regarded this factory as "too unhealthy" and was "taking no chances." Only walnut and Western cedar woods were used, and the recurrence of symptoms are assumed to have been due to the inhalation of Western cedar dust, as he knew from experience that the former did not affect him.

In January, 1948, the patient found employment in another factory where he has continued working up to the present (October, 1948). The woods used are kejaat, walnut and birch. He has had no asthma, but every few weeks he develops persistent "colds" characterized by sneezing and running of the nose. Otherwise the patient is in very good health, has gained weight and feels like a "new man."

In summary, therapeutic desensitization was commenced in October, 1946. His condition rapidly improved, and two months later he became completely free from asthma and remained so for more than a year under unchanged conditions of work. Unfortunately, no fresh wood extracts were made available to the patient during the writer's absence overseas, and the recurrence of allergic symptoms—vasomotor rhinitis but no asthma—was not altogether surprising. It is proposed to resume desensitization with fresh wood extracts.

SUMMARY

1. A case of asthma is described in a cabinet maker of Bantu-Chinese stock which was found to be etiologically associated with the inhalation of wood dust in the course of his work.

2. The woods to which the patient was found sensitive, confirmed by skin tests, were kejaat (*Pterocarpus angolensis*), Western red cedar (*Thuja plicata*) and Congo hardwood.

3. Therapeutic desensitization rapidly produced complete relief from asthma and other allergic symptoms with relatively few injections of graded doses of the combined wood extracts. With further monthly injections of the extracts, the patient was able to maintain this symptomless state for more than a year, although his working conditions remained unchanged.

REFERENCES

1. Bahn, K.: Beitrag zur Frage der Allergie bei Holzagereiarbeiten. Klin. Wchnschr., 7:1963, 1928. Quoted from Feinberg, S. M., Durham, O. C., and Dragstedt, C. A.: Allergy in Practice. Second ed. Chicago: Year Book Publishers, 1946.
2. Cobe, H. M.: Sensitivity due to Christmas trees: a seasonal atopen in bronchial asthma. J. Allergy, 1:442, 1930.
3. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and hay fever in theory and practice. Springfield: Charles C. Thomas, 1931.
4. Davidson, J. M.: Toxic effects of iroko; an African wood. Lancet, 1:38, 1941.
5. Markin, L. E.: Boxwood sensitiveness. J. Allergy, 1:346, 1930.
6. Piorkowski, F. O.: Woodworkers dermatitis in East Africa. East African M. J., 21:60, 1944.

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ANNALS of ALLERGY

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CHRONIC ULCERATIVE COLITIS—AN ALLERGIC DISEASE

ALBERT H. ROWE M.D., F.A.C.A.
Oakland, California

FOR twelve years this writer[13] has gathered evidence that an erythematous, eczematous-like, inflammatory reaction due to food, and less often to pollen and other inhalants and to drug allergy, is the primary cause of chronic ulcerative colitis. Allergy to bacteria and the Sanarelli-Schwartzman reaction also need study, though evidence for this now is lacking.

When allergy is the sole cause, the symptoms and tissue changes gradually reduce or disappear with control of the allergies. When complicating infection, anemia, hypoproteinemia or avitaminosis are present, their treatment along with the control of the allergies is necessary for good results. Severe or fulminating ulcerative colitis can be due to marked food and/or inhalant and possibly drug allergy, with or without the above secondary complications.

Andresen[2] in 1931 first suggested food allergy as the cause of chronic ulcerative colitis. In 1942 he confirmed this opinion in an extended article. Mackey,[9] in 1938, stressed food allergy in the production of this disease, but felt that it was of secondary importance to other major influences. This writer reported allergy especially to foods as the major cause in 1942, and for the first time pollen allergy was found to be responsible for the disease. Other inhalants also were suggested as probable major causes. Since then, confirmation of allergy to foods and less often to pollens was published in 1944,[14] 1947,[17] 1948,[18] and 1949[20] by this writer.

The following favor allergy as a primary cause:

1. Gastrointestinal allergy,[11,13] usually to foods, is very frequent, occurring in any part of the tract from the mouth to the rectum and anus. Local passive transfer in the mucosa of the rectum ileostomies and colostomies have been reported by Gray and Walze[6] and others. Oral and pharyngeal allergy and gastric allergy are common in our experience. Al-

From the medical department of the University of California Medical School, San Francisco, California.
Supported in part by the Armour-Gerber Fund and the Hackett and Creed Funds for research. Gerber and Co. furnished much of the strained meats used in these studies.

147. Davis, D.: Inhalation of penicillin aerosol and penicillin-streptomycin. Arch. Otolaryng., 46:307, 1947.
148. Davy, J., and Thibault, C.: New amines opposing the action of adrenalin on bronchi. Bull. Soc. Chim. Biol, Paris, 28:114, 1946.
149. Dees, S. C., and Lowenbach, H.: Electro-encephalograms of allergic children. Ann. Allergy, 6:99, 1948.
150. Delafontaine, P., and Pistre, M.: Intermittent nitrogen retention accompanying attacks of asthma. Presse Méd., 55:682, 1947.
151. Dell, J. M.: Bronchography. South. M.J., 40: July, 1947.
152. De Martini, A.: Differential diagnosis between transitory pulmonary infiltrations and cystic emphysema. Roentgenologic study. Minerva Med., 1:58, 1947.
153. Dernehl, C. U.: Potential pathologic significance of dusts found in Texas industry. 43:4, 1947.
154. Diaz, Rivera, R. S., Garaua, S., and Porrata, I. L.: Löffler's syndrome. Bol. Assoc. Med. ed Puerto Rico, 39:315, 1947.
155. Dickie, H. A.: Spontaneous mediastinal emphysema and spontaneous pneumothorax. Ann. Int. Med., 28:618, 1948.
156. Dickie, H. A., and Clark, E. A.: Histoplasmin and tuberculin sensitivity in relation to pulmonary calcification among University of Wisconsin students. Ann. Int. Med., 28:1087, 1948.
157. Dumm, J. F., and Zarate, O.: Use of aerosols in allergic patients. Allergia, 1:791, 1947-8.
158. Donoso, R., Cumsille, F. E., and Donoso, D.: Procaine hydrochloride in asthmatic crises. Rev. Clin. Espaü., 24:342, 1947; and Rev. Méd. de Chile, 75:96, 1947.
159. Dragstedt, C. A.: Idiosyncrasy to drugs. J.A.M.A., 135:133, 1947.
160. Duchaine, J.: Medico-social treatment of asthma in children. Arch. belg. de Méd. Sociale, Hygiene, Méd. du travail et Méd. legale, 6:7, 1948.
161. Duerfeldt, T. H.: Acute Benadryl poisoning. Northwest Med., 46:781, 1947.
162. Dugaujon, F., and Mallet, R.: Tuberculous asthma. J. de Méd. de Bordeaux, 124:500, 1947.
163. Durham, O. C.: Our national parks as ragweed hay fever refuges. J.A.M.A., 138:126, 1948.
164. Durham, O. C.: Ragweed pollen incidence 1947. J. Allergy, 19:343, 1948.
165. Durham, O. C.: The volumetric incidence of atmospheric allergens. V. Spot Testing in the Evaluation of Species. J. Allergy, 18:231, 1947.
166. Dutton, L. O.: Comparative diagnostic efficiency of the sedimentation rate and the weltman reaction. Ann. Allergy, 5:491, 1947.
167. Dutton, L. O.: Mold fungi in etiology of respiratory allergic diseases. VI. Intrinsic fungous factors in relation to asthma. Ann. Allergy, 5:439, 1947.
168. Dwyer, H. V.: Treatment of the common respiratory infections. J. Michigan Med. Soc., 46:1407, 1947.
169. Editorial: New England J. Med., 237:411, 1947.
170. Editorial: Physiology of the lungs and asthmatic state. Ann. Allergy, 6:63, 1948.
171. Egbert, O. E.: Reversing influence of low humidity on intractable asthma. Acta Allerg. K.B.H., 1:224, 1948.
172. Eisenstadt, W. S.: Incidence and significance of molds in allergic respiratory symptoms. Journal Lancet, 68:217, 1948.
173. Elkeles, A., and Butler, N. R.: Transitory pulmonary infiltration and apical association with eosinophilia. Brit. J. Radiol., 19:512, 1946.
174. Engelsher, D. L.: Antihistamine drugs in asthma and hay fever. New York State J. Med., 47: Aug. 1, 1947.
175. Epstein, B. S., Sherman, J., and Walzer, E.: Bronchography in asthmatic patients with the aid of adrenalin. Radiology, 50:96, 1948.
176. Farrerons-Co, F. J.: Universal classification and terminology of allergic diseases. Medicina, Madrid, 15:435, 1947.
177. Feinberg, S. M.: Allergic problems of the railway surgeon. Indust. Med., 17:91, 1948.
178. Feinberg, S. M.: The antihistaminic drugs. Am. J. Med., 3:560, 1947.
179. Feinberg, S. M., and Bernstein, T. B.: Histamine antagonists. J. Lab. & Clin. Med., 32:1370, 1947.
180. Feinberg, S. M.: Histamine antagonists. Quart. Bull. Northwestern Univ. M. School, 22:27, 1947.
181. Feinberg, S. M., and Bernstein, T. B.: Histamine antagonists (Decapryn succinate). J. Lab. & Clin. Med., 33:319, 1948.
182. Feinberg, S. M.: Newer drugs in treatment of allergic diseases. Post-grad. M.J., 3:92, 1948.
183. Feinberg, S. M.: Therapy of asthma. Facts and fancies. Illinois M.J., 92:234, 1947.
184. Fineberg, S. K.: Anaphylactic shock due to nicotinic acid. New York St. J. Med., 48:635, 1948.
185. Finke, W.: The rationale of penicillin aerosol therapy in bronchopulmonary infections. Bull. Med. Soc., Rochester, N. Y., 5:9, 1947.
186. Finlayson, M. H.: Laboratory contributions to etiology and treatment of allergic asthma. South African M.J., 21:724, 1947.
187. Fischer, R.: Non-specific desensitization by scorpion venom. Acta med. orient., 6:127, 1947.
188. Flensborg, E. W., and Samsoe-Jensen, T.: Mold spore counts in outside air in Copenhagen. Acta Allergologica, 1:104, 1948.
189. Font, J. H.: Eosinophilic lung. Ann. Otol., Rhin., & Laryng., 56:804, 1947.
190. Forman, F.: Certain clinical aspects of asthma. South African M.J., 21:722, 1947.
191. Forman, J.: Directory of physicians interested in clinical allergy, pp. 176. International Correspondence Society of Allergists, 956 Bryden Road, Columbus, Ohio, 1948.
192. Frank., R.: Study of a new histamine antagonist. Ann. Allergy, 6:398, 1948.
193. Franklin, H. L.: Aminophyllin with a barbiturate as rectal suppository. New York St. J. Med., 47:1242, 1947.
194. Fried, B. M.: Bronchogenic adenoma. Arch. Int. Med., 79:291, 1947.
195. Friedlaender, A. S., and Friedlaender, S.: An evaluation of Antistine. Ann. Allergy, 6:23, 1948.
196. Friedlaender, A. S., and Friedlaender, S.: Antihistaminic, antianaphylactic and anti-allergic activity of Thenylene. Am. J.M. Sc., 215:530, 1948.
197. Friedlaender, S., and Friedlaender, A. S.: Newer antihistaminic drugs in symptomatic treatment of allergic manifestations. Am. Practitioner, 2:643, 1948.
198. Friedlaender, S., and Friedlaender, A. S.: Parenteral Benadryl in allergy. Am. J. Med., 4:863, 1948.
199. Friedman, M.: Studies concerning the etiology and pathogenesis of neuro-circulatory asthenia. Psychosom. Med., 9:233, 1947.

lergic reactions in various parts of the small and large bowel account for colic, cramping, diarrhea, bleeding, abdominal soreness and pain, fever and other symptoms with varying frequencies. This writer has observed cases of regional enteritis controlled by the elimination of allergenic foods alone. Our experience also indicates that mucous colitis, the irritable bowel, soreness in the colon, constipation and diarrhea, rectal and anal soreness and spasm, a predisposition to hemorrhoids, pruritus ani and a secondary fistulae and abscesses are frequently due to allergy, especially to foods. Psychosomatic causes too frequently are blamed for these symptoms.

2. Allergy best explains the primary lesions of this disease. The erythema, edema and easy bleeding can result from vascular allergy, as they do in atopic eczematous dermatitis. The mucosal granulation similar to that in the skin of atopic eczema is best explained by the multitudinous minute amounts of serum exuding into the mucosa from the allergenically inflamed capillaries. The clinical characteristics, course, and response to proper allergic treatment of cases of atopic dermatitis due to food pollen and other inhalant and drug sensitivities should be observed by all physicians who wish to understand the role of allergy in chronic ulcerative colitis. This continuous serous exudation from the allergically inflamed mucosa and the oozing of blood from the dilated capillaries in the mucosa increase hypoproteinemia.

The herpetic ulcers can arise from minute vascular thromboses, similar to those which cause oral canker sores, which in practically all cases are due to food and at times to drug and bacterial allergies. Also autodigestion by pancreatic enzymes rushed into the colon by hyperperistalsis may enlarge those ulcers and produce denudation of mucosa, perforation, bleeding or gross hemorrhage.

When resistance to infection is low, infection of the mucosa, fever, abscesses, fistulas, perforation and peritonitis may occur. When resistance is high, the allergic colitis can continue in varying degrees with no complications or fever due to infection.

3. Chronic allergy can produce scar tissue. This is evidenced especially in the permanent scarring of the corneas from recurrent corneal ulcers with persistent inflammation due to food allergy observed by this writer. Thus, allergy with or without secondary infection may cause irreversible fibrosis, narrowing or stricture in the colon.

4. Remissions can be explained by the tendency for clinical allergy to cease or decrease without apparent cause. Refractoriness to the allergic reaction after a severe allergic attack of asthma or allergic headache or chronic ulcerative colitis is best explained by the exhaustion of specific reacting bodies in the shock tissues or temporary failure of production of such bodies. Thus even though causative allergens of foods or inhalants are ingested or inhaled, the allergic manifestation is minimal or absent.

The decrease or absence of food allergy during the summer months, long reported by this writer,[21] can explain temporary remissions in some

257. Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output, etc., in cardiovascular disease and emphysema. J. Clin. Investigation, 27:10, 1948.
258. Hill, F. T.: Atelectasis in the new born. Ann. Otol. Rhin. & Laryng., 57:220, 1948.
259. Hill, L. W.: Food sensitivity in 100 asthmatic children. New England J. Med., 238:657, 1948.
260. Hillemand, P., Derot, P., and Brule, G.: Megalogastria disappearing after ephedrine therapy. Bull. et Soc. Med. & Hôp. de Paris, 63:384, 1947.
261. Holinger, P. H.: Bronchial obstruction. Mississippi Doctor, 25:313, 1948.
262. Holinger, P. H., Andrews, A. H., Jr., and Anison, G. C.: Pulmonary complications due to endobronchial foreign bodies. Illinois M.J., 93:19, 1948.
263. Horesh, A. J.: Allergy in children. Clinics, 5:678, 1946.
264. Horstman, P., and Kjerulf-Jensen, K.: Dyspnea provoked by histamine in patients with bronchial asthma. Nord. Med., 34:910, 1947.
265. Huff, D. H.: Bronchial asthma simulated by a foreign body in the bronchus. Balycat Asthma and Hay Fever Clin. Proc., 17:17, 1947.
266. Huff, D. H.: Massive atelectasis of the lower lobe due to a mucous plug in a major bronchus. Balycat Hay Fever & Asthma Clin. Proc., 17:12, 1947.
267. Huff, R. H.: Iodide sensitivity manifested by tenderness and swelling of the breasts. Balycat Hay Fever and Asthma Clin. Proc., 17:19, 1947.
268. Infants, R: Bronchiectasis responsive to aerosoltherapy. Arch. Hosp. Clinica de Niños, Santiago, Chile, 15:82, 1947.
269. Irigoya Freyre, A.: Asma Bronquial, diagnóstico y tratmiento broncoscopico Día. méd., 19: 211, 1947.
270. Jacquelin, A., Turiaf, J., Mace de Lapinay, A., and Dubois: Is asthma no more than a syndrome? Le Bull. Méd., 61:33, 1947.
271. Jiménez-Díaz, C., Arjona, E., Alés, J. M., Grande, F., López-García, and Oya, J. C. Mechanism of asthmatic crisis. Rev. clin. españ., 7:207, 1946.
272. Jiménez-Díaz, C., Lahoz, C., and Canto, G.: Allergens of mill dust: asthma in millers, farmers and others. Ann. Allergy, 5:53, 1947.
273. Jiménez-Díaz, C., and López García, E.: Fatal asthma; mechanism of asthmatic crisis. Gac. méd., Lima, 3:52, 1947.
274. Jolicoeur, A.: Asthma associated with ovarian disturbance. Canad. M.A.J., 58:188, 1948.
275. Kallos, P.: Significance of histamine antagonists in treatment of allergic disease. J.A.M.A., 135:315, 1947.
276. Karns, J. R., and Daue, E. O., Jr.: Mediastinotomy in spontaneous mediastinal emphysema. J.A.M.A., 136:622, 1948.
277. Katz, K. H., and Chandler, H. L.: Morphine sensitivity in kyphoscoliosis. New England J. Med., 238:322, 1948.
278. Kay, E. B.: Actinomyces in broncho-pulmonary infections. Am. Rev. Tuberc., 57:322, 1948.
279. Kern, R. A.: Perennial allergic rhinitis. Saunders Co., Philadelphia.
280. Kleckner, M. S., Jr.: Clinical appraisal of Benadryl, Pyribenzamine and Anthallan. Ann. Int. Med., 28:583, 1948.
281. Klein, A.: Spontaneous emphysema with acute right ventricular strain. Am. Heart J., 33:867, 1947.
282. King, F. H.: Protracted course in periarteritis nodosa. J. Mt. Sinai Hosp., 15:97, 1948.
283. K. N.: Treatment of bronchial asthma. Praxis, Bern., 37:638, 1948.
284. Koelsche, G. A.: Aerosol therapy. J. Allergy, 19:47, 1948.
285. Koelsche, G. A.: Present management of hay fever. Proc. Staff Meet., Mayo Clin., 22:337, 1947.
286. Kohn, J. L.: Penicillin sensitivity. Bronchial spasm. J. Mt. Sinai Hosp., 14:460, 1947.
287. Korol, E.: Cystic and bullous emphysema of lungs. Dis. of Chest, 13:669, 1947.
288. Krasno, L., Karp, M., and Rhoads, P. S.: Inhalation of penicillin dust. Science, 106: 249, 1947.
289. Kurkijarir, M.: Eosinophilia and tuberculosis. Nord. Med., 4:3717, 1939.
290. Laipply, T. C.: Polyarteritis nodosa, review. Am. Pract., 2:795, 1948.
291. Lange, K.: Surgical therapy of bronchial asthma. Schweiz. med. Wchnschr., 76:228, 1946.
292. Leger, J.: Antihistamine medication. Synthetic agents. Union méd. du Canada, 77:5, 1948.
293. Lehmann, C. F.: Löffler's syndrome with erythema multiforme. Southern M. J., 41:37, 1948.
294. LeMone, D. V., Scott, W. G., Moore, S., and Kouen, A. L.: Bagasse disease of the lungs. Radiology, 49:556, 1947.
295. Letter from Italy: Myocardial infarction following intravenous injection of epinephrine, J.A.M.A., 137:1077, 1948.
296. Levin, S. J., and Moss, S. S.: Hydryllin in bronchial asthma and hay fever. J. Michigan Med. Soc., 47:869, 1948.
297. Levinton, J.: Athletic activity of asthmatic. Semana méd., 1:663, 1947.
298. Levy, L., II, and Seabury, J. H.: Spirometric evaluation of benadryl in asthma. J. Allergy, 18:244, 1947.
299. Levy, L., II, and Seabury, J. H.: Spirometric evaluation of ethyl-nor-epinephrine in bronchial asthma. J. Allergy, 19:58, 1948.
300. Levy, S. B.: Asthma due to ingestion of fennel and fennel seed. Ann. Allergy, 6:415, 1948.
301. Lewi, W. G.: Asthma and hay fever. Clin. Med., 54:402, 1947.
302. Linko, E.: Allergic rhinitis and bronchial asthma in bakers. Ann. Med. Int. Fenn., 36:98, 1947.
303. Little, A. S., and Little, R. P.: Prevention of asthma. Hygiea, 26:192, 1948.
304. Livingston, S.: Sedimentation rates with asthma. Bull. Johns Hopkins Hosp., 82:385, 1948.
305. Llaudet, J. P.: Bronchiectasis. Med. Clínica, 9:381, 1947.
306. Lockey, S. D.: Benadryl: A clinical evaluation. Ann. Allergy, 5:420, 1947.
307. Loeffler, W.: Zur Pathogenese und Etiologie der Eosinophilen Rungennfitrate. Praxis (Bern), 37:55, 1948.
308. Loeper: Cinchofen in bronchial asthma. Monde Méd., 57:986, 1947.
309. Loesches, H.: Treatment of bronchiectasis and bronchial suppuration by intracheal injections of penicillin. Dis. of Chest, 13:533, 1947.
310. Loew, E. R.: Pharmacology of antihistamine compounds. Physiol. Rev., 27:542, 1947.
311. Löffler, W., Esselier, A. F., and Macedo, M. E.: Löffler's syndrome, pathogenesis, etiology. Helvetica Med. Acta (Basel), 15:223, 1948. (partial index)
312. Logan, G. B.: Histamine antagonists in treatment of allergic diseases in children. M. Clin. North America., 31:948, 1947.
313. Logan, G. B.: Management of allergic disease of the respiratory tract in children. Pennsylvania M. J., 51:739, 1948.

food-sensitive patients. And the decrease or absence of symptoms in the seasons, especially the winter when the allergenic pollens are out of the air, causes partial or complete relief from chronic ulcerative colitis due to pollen allergy. Temporary or intermittent ingestion or inhalation of allergic substances, moreover, can explain irregular exaggerations of ulcerative colitis.

5. Localization of this disease in the rectum or other parts of the colon is better explained by allergy than by infection. The spreading tendency of atopic dermatitis is well known and probably exists in the allergic colon, explaining the extension of chronic ulcerative colitis in many patients.

6. Fever may be due to food allergy alone.[19] Usually a secondary infection is responsible.

Thus allergy must receive adequate and experienced study as the probable major cause of all cases of this disease. The colon may be the only shock organ of allergy, though manifestations of allergy in other tissues may exist. Carefully taken dietary histories may reveal dislikes or disagreements to foods, especially to milk. Such histories may or may not indicate clinical allergy. Negative histories, moreover, do not rule out food sensitization. As in most chronic food allergy, skin reactions to allergenic foods are rarely positive, emphasizing the necessity of diet trial for the study of such sensitization. Inhalant allergy should be suspected when its other manifestations are present, and when definite positive skin reactions are obtained. The colon may be the only shock tissue of pollen allergy. The occurrence of inhalant allergy without skin reactions in about 10 to 15 per cent of all inhalant-sensitive individuals also must be remembered.

TREATMENT

Our treatment, therefore, considers allergy in all patients in the following manner:

1. For the study of possible food allergy in mild or moderate cases the writer's fruit and cereal-free elimination diet[16] is preferred. Lamb usually is the only allowed meat. Possible allergy to beef when sensitization to milk is present or assumed must be suspected. Ample amounts of food in the menus are necessary. The patient should be weighed every two days. More of the starch, sugar and, to a lesser extent, fat in the diet should be taken by the patient if weight lessens. Trays should not be removed until most or all the served food has been ingested. Protein can be increased up to 75 to 120 grams a day by giving one to five cans of Gerber's or Swift's strained lamb daily, especially if hypoproteinemia is present. The included vegetables may be pureed, but when allergy is brought under control, this may not be necessary. In the initial studies the vegetables can be eliminated entirely, especially if improvement does not occur in seven to ten days. Calcium carbonate, 2 grams, and ascorbic acid, 50 mg. a day, are advisable.

Improvement usually is apparent in three to fourteen days. When assured, rice, rye and corn can be added, giving one daily for five to seven

373. Pascucci, L. M.: Pulmonary disease in workers exposed to beryllium compounds. Radiology, 50:23, 1948.
374. Pearlman, A. W.: Löffler's syndrome. Am. J. Roent. & Rad. Therapy, 58:75, 1947.
375. Pedrazzini, A.: Löffler's syndrome. Minerva Med., 2:61, 1947.
376. Pellerat, J., Nurat and Sauvageot, G.: Action de antihistaminique dérivés de la Thiodiphenyl-amine, sur l'histamine. C. Rend. Soc. Biol., 142:5, 1948.
377. Pennington, E. S.: Allergic conditions in infants and children. Am. J. Nursing, 46:85, 1946.
378. Pennock, L. L.: Advances in treatment of allergy. Pennsylvania M. J., 50:609, 1947.
379. Pepys, J.: Skin tests in asthma. S. African M.J., 21:729, 1947.
380. Peralta, O. E., and Valle, L. R.: Anamnesis of asthmatic. Día. Méd., 19:671, 1947.
381. Peshkin, M. M., and Rapaport, H. G.: Immunity to diphtheria induced by a booster dose of diphtheria toxoid purified by absorption and elution. Based on a Study of fifty-five Allergic Children. Ann. Allergy, 5:503, 1947.
382. Peters, J.: Thephorin, a new antihistamine, Illinois M. J., p. 314, June, 1948.
383. Peterson, H.: Fatal case of bronchial asthma complicated by mediastinal and subcutaneous emphysema. J. Allergy, 18:413, 1947.
384. Philps, A. S.: Asthma, eczema, cataract. Proc. R. Soc. M., London, 40:13, 1947.
385. Pierce, J. D., and Mothersill, M. H.: Treatment of allergic symptoms with histadyl. J. Indiana M. A., 40:739, 1947.
386. Piness, G.: What is new in allergy? California Med., 67:291, 1947.
387. Piness, G., Tuft, L., Eyerman, C. H., Cooke, R. A., and Black, J. H.: Treatment of asthma. A panel discussion. J.A.M.A., 37:453, 1948.
388. Plummer, A. J.: A method for quantitative estimation of theophyllin in blood and urine. Application to the dog. J. Pharm. & Exper. Therap., 93:142, 1948.
389. Poe, W. D.: Fatal coronary artery disease in young men. Bull. U.S. Army Med. Dept., 7:394, 1947.
390. Pool, B. B., Harrill, J. A., and Rousseau, J. P.: Irradiations for lymphoid hyperplasia and allergic bronchial asthma. North Carolina M. J., 9:84, 1948.
391. Pool, J. L.: Diagnostic difficulties in intrathoracic neoplasms. New York State J. M., 48:895, 1948.
392. Poppe, J. K.: Lung disease. Diagnostic significance of clubbed fingers. Dis. Chest, 13:658, 1947.
393. Pounders, C. M.: The allergic child. Southern M. J., 41:142, 1948.
394. Powers, B. R.: Observation on use of Demerol. Southern M. J., 40:870, 1947.
395. Press, E.: Desirability on routine use of tetanus toxoid. New England J. M., 239:50, 1948.
396. Prickman, L. E., and Morgan, J. L.: Intolerance to common drugs administered for asthma. Proc. Mayo Clin., 22:391, 1947.
397. Prigal, S. J.: Treatment of asthma. J.A.M.A., 138: (Sept. 4), 1948.
398. Prigal, S. J., McGavack, T. H., Speer, F. D. & Harris, R.: Aerosol penicillin. J.A.M.A., 134:932, 1947.
399. Prigal, S. J.: Studies with medicated aerosols. Ann. Int. Med., 28:814, 1948
400. Prigal, S. J., Morganbesser, L. J., and McIntyre, F. P.: Penicillin aerosol in the prevention and treatment of respiratory infections in allergic patients. J. Allergy, 18:325, 1947.
401. Prigal, S. J., McGavack, T. H., and Bell, M.: The effect of propylene glycol on the antibiotic activity of human serum. Am. J. of M., 3:185, 1947.
402. Rackemann, F. M.: Is asthma a symptom or a disease? Rhode Island M. J., 30:657, 1947.
403. Rackemann, F. M.: Editorial. J. Allergy, 18:351, 1947.
404. Rackemann, F. M.: Nurse and patient with asthma. Am. J. Nursing, 47:463, 1947.
405. Rackemann, F. M.: The Doctor and the patient with asthma. Bull. Chicago M. Soc., 50.812, 1948.
406. Rackemann, F. M.: Working classification. Am. J. M., 3:601, 1947.
407. Randolph, T. G.: Management of food allergy. M. Clin. N. Amer., 32:245, 1948.
408. Rawlins, A. G.: Chronic allergic sinusitis (perennial nasal allergy). Laryngoscope, 57:381, 1947.
409. Reiser, M. F., and Ferris, E. B., Jr.: Use of respirator in respiratory status asthmaticus. Ann. Int. Med., 29:64, 1948.
410. Reymann, F., and Schwartz, M.: House dust and fungus allergy. Acta Path. et Microbiol. Scand., 24:76, 1947.
411. Report Committee Therapy, A.A.A., Neo Antergan. J. Allergy, 18:352, 1947.
412. Reynolds, J. L., and Horton, B. T.: Clinical observation on use of Thephorin. Proc. Staff Meet. Mayo Clin., 22:574, 1947.
413. Rice, D. A., and Scott, J. W.: Löffler's syndrome. Canada M.A.J., 57:286, 1947.
414. Richard, B. L.: Relationship between bronchial asthma and tuberculosis. Ap. Resp. & Tuberc., Santiago, 13:17, 1948.
415. Riddell, A. R.: Pulmonary dust diseases. Indust. Med., 17:168, 1948.
416. Riley, R. L.: The differentiation of cardiac and pulmonary dyspnea. American Heart Association Vol. 17 (July), 1948.
417. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournard, A.: Studies of pulmonary circulation in normal individuals and in chronic pulmonary disease. Am. J. Physiol., 152:372, 1948.
418. Rimington, C., Stillwell, D. E., and Maunsell, K.: Allergens of house dust. Purification and chemical nature of active constituents. Brit. J. Exper. Path., 28:309, 1947.
419. Roberts, E. A.: A new development in antihistaminic therapy. Indust. Med., 17:263, 1948.
420. Roberts, W. G.: Protecting your child from allergy. Hygiea, 25:602, 1947.
421. Robson, K.: Medical contraindications to flying. Practitioner, 160:459, 1948.
422. Roche, L., and Ode, L.: Emphysema during silicosis. Presse Méd., 55:656, 1947.
423. Rockwell, G. E.: Histamine derivatives with prolonged action. Ann. Allergy, 6:353, 1948.
424. Rodriguez, Candela, J. L.: Synthetic antihistamine substances and their therapeutic use. Medicina Madrid, (part II), 15:151, 1947.
425. Rose, B.: Role of histamine in anaphylaxis and allergy. Am. J. Med., 3:545, 1947.
426. Rosen, F. L.: Sensitivity to streptomycin; anaphylactic shock with recovery. J.A.M.A., 137:1128, 1948.
427. Rosenberg, M. H., and Blumenthal, L. S.: Use of intravenous Benadryl Am. J. M. Sc., 216:159, 1948.
428. Rosillo, M., and Pla, J. C.: Magnesium sulfate in bronchial asthma. Monde Méd., 57:991, 1947.
429. Rowe, A. H., and Rowe, A. H., Jr.: Bronchial asthma in infants and children. California Med., 69:261, 1948.
430. Rowe, A. H., and Rowe, A. H., Jr.: Bronchial asthma in patients over age of fifty-five: diagnosis and treatment. Ann. Allergy, 5:509, 1947.

days before trying another. Later egg, wheat and other individual vegetables and cooked fruits gradually may be added. Since milk is the most common cause of colonic allergy it should be omitted for weeks or even months. This is especially important if a distaste or disagreement for milk has occurred at times for years. With ample protein in meat, calories in sugar, starches and fats in the diet and the prescribed calcium, milk can be excluded for months or years without nutritional deficiency. If symptoms recur the recently added foods must be excluded.

The prolonged exacerbations of ulcerative colitis (see Case 3) in some patients, arising from allergenic foods ordered by this writer or eaten against orders, together with the associated resultant infection, bleeding and anemia which may arise, deter further trial of such foods in well-controlled patients. Thus such allergenic foods, especially milk, have been eliminated entirely from the diets of many of the writer's patients for several years (see case reports), and no nutritional impairment has resulted.

If improvement does not occur in two weeks, and food allergy is definitely suspected, a minimal elimination diet of lamb, white potato, sugar, tapioca, noniodized salt and water can be ordered. In order to maintain nutrition and weight, feedings of this diet may be given four to six times a day. Along with lamb chops, roast and minced lamb, a can of the strained lamb three to six times a day can be given. Thus this minimal diet readily contains from 70 to 120 grams of protein and 2,000 or more calories each day. Vitamin therapy is discussed below.

In fulminating cases, especially with nausea and anorexia, the following formula[14] can be given every two and one-half to three hours throughout the day. Because of the frequency of milk allergy, beef is not allowed until symptoms are well controlled. Diarrhea and also fever have recurred with its use in a few patients.

Strained Meat Liquid Formula for Chronic Ulcerative Colitis (Rowe)

Gerber's or Swift's strained lamb	8 cans or 800 gm.
Soy oil	53 c.c.
Sugar, cane	170 gm.
Potato starch	30 gm.
Salt	2 tsp. or 8 gm.
Calcium carbonate	½ tsp. or 2 gm.
Water	qs. 2000 c.c.

Protein, 128 gm. Calories, 2000

Cook the starch, salt and sugar in 1 cup of water for 10 minutes. Then add the meat and oil, and cook with low heat for 10 to 15 minutes. Reduce the amount of starch to yield a thinrer product.

Along with this formula, white potato, tapioca or arrowroot cooked with sugar, caramel and salt, white potato as such, lamb, water and salt may be given three to four times a day. This formula may be fed by nasal intubation in 200 to 300 c.c. amounts every three to four hours if nausea is persistent and anorexia is marked. With definite improvement other foods may be added as suggested above.

In the treatment of allergy with antihistaminics it is essential to assure the patient a continuous, uniformly high degree of protection. Too rapid excretion or detoxification of the drug inevitably leads to a fluctuating, unreliable status, alternating between full protection and complete vulnerability. Chlorothen, Whittier, is distinguished pharmacologically by its prolonged action. Clinically, therefore, each dose may be relied upon to maintain a greater protective effect for a longer dosage interval—a constant defensive shield against allergens.

POLLEN AND OTHER INHALANT ALLERGY

2. When pollen and other inhalant allergy is indicated by history or skin tests, desensitization, as recently advised by the writer, and strict environmental control, including a pollen filter in the window, are indicated. Pollen, dust and other inhalant allergy should also receive thorough study in patients suspected of food allergy if diet trial does not produce results in two to four weeks. As in atopic dermatitis due to pollen and other inhalants, desensitization[16] is necessary with multiple antigens in dilutions weak enough to produce gradual improvement and no exaggeration of symptoms. Coseasonal therapy especially requires a careful and often slow increase of very dilute antigens. With definite improvement, stronger dilutions gradually can be injected. Desensitization must be perennial, and continued in such pollen-sensitive patients for at least two years and usually for longer periods.

3. Vitamin therapy is important. Vitamin C, 50 to 100 mg., daily, Drisdol and synthesized B complex vitamins by mouth are advisable. If avitaminosis is definite, then vitamins B and C may be given parenterally. Allergy to vitamin C[19] may occur with sensitization to all or practically all fruits. Occasional allergy to thiamin and possibly to other vitamins in the B complex must be remembered (see Case 3). Crude liver extract intramuscularly may be more helpful than the above vitamins in relieving B vitamin deficiency. Moreover, it may produce a beneficial nonspecific action.

4. Transfusions and iron, if tolerated by mouth, are indicated for anemia.

5. For bleeding, transfusions, vitamin K, if indicated, and possibly rutin are advisable.

6. For hypoproteinemia, transfusions and irradiated plasma are indicated. The protein in the diet can be increased up to 150 gm. a day with the use of Swift's or Gerber's strained lamb, either as such or in the above formula. This decreases the necessity of amino acids by mouth and vein which are less efficiently utilized than are food proteins by mouth. Possibility of allergy to milk and pork allergens in trypsin-digested amino acids and their disagreeable taste, moreover, contraindicate their use in this disease. The good results with enzymatic casein digest and dextri-maltose reported by Machella[8] require the consideration of relief of causative food allergy.

7. Aspirin, codeine and at times tincture of opium are necessary for pain and cramping. Other antispasmodic drugs are disappointing, supporting Alvarez's opinion[1] that such drugs, including atropine, are relatively ineffectual in controlling spasm in the bowel. Some relief from cramping from antihistaminic drugs in some patients supports the allergic etiology.

8. Duodenal extract was not used to obtain our good results. In three patients it was distasteful, and caused nausea, anorexia or diarrhea.

9. Barbiturates for nervousness and sleep are justified. They should

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be taken only when necessary and never in amounts productive of stupor or confusion. Allergy to them or the excipients may occur.

10. When secondary infection occurs or is probable, sulfadiazine by mouth may be valuable. Sulfaquanidine, sulfathalidine or sulfasuxidine in larger doses occasionally aid.

Svartz[21] and recently Bargen[1] have reported good or excellent results from a new preparation Salicylazosulfa pyridine (Salazopyrin). This has been confirmed in a few of our patients.

Allergy to all of these drugs may exist, or develop during their use, causing fever, nausea, cramping, increased diarrhea, skin eruptions and other symptoms.

11. In one of the writer's cases 1 gm. of streptomycin four times a day by mouth controlled persistent fever in two days. Aureomycin and Chloramphenicol (Chloromycetin) in .25 to .5 gram doses produced similar results. The dose should be reduced to .25 gm. three to five times a day as soon as fever has ceased. Allergy and especially toxic symptoms from these drugs must be anticipated. Aureomycin[10] seems preferable if tolerated because of its under antibacterial activity. When this is not tolerated, Chloramphenicol often is effective.

12. To increase resistance to infection, stock streptococcic, staphylococcic, Bargen bacilli or respiratory vaccines at times may be valuable. Benefit from an autogenous hemolytic staphylococcic vaccine has been reported. These vaccines should be started with dilutions of 1:10,000 to 1:1,000,000, anticipating possible allergic reactions thereto. Rapid increase through the 1:1,000 and 1:100 and 1:10 dilutions is justified every three to four days if local or general reactions and increase in the colitis do not develop. Abnormal susceptibility or allergy to such vaccines occurs in some patients, producing a local reaction suggestive of a possible Arthus type of reaction.

13. Reassurance of the patient, based on the good results obtained with the above therapy, is important and justified. Nervous disturbances in severe cases, we believe, are the result rather than the cause of this disease. As in other types of allergy, nervousness can activate a potential allergy in the colon. The production of the severe pathologic condition of chronic ulcerative colitis by psychosomatic causes is illogical in our opinion.

SURGERY

Ileostomy or colostomy should not be done without adequate treatment based primarily on the probability that food and/or inhalant allergies are the major causes of an eczematous-like reaction in the colon. With elimination diets as here advised, nutrition and weight can be maintained and gradually increased for many weeks while these food and inhalant allergies are being studied and treated, and complicating infection, hypoproteinemia and anemia are being controlled. Only when perforation and peritonitis threaten, or when perianal abscesses and infection with fever increase in spite of this adequate treatment, is surgery justifiable. At present the

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lowered mortality from ileostomy due to antibiotics, together with the prevalent uncertainty about the cause of this disease, is responsible for "early ileostomies" in many patients with chronic ulcerative colitis which, in our opinion, could be controlled as here advised. Subsequent complete colectomy, usually in two stages, with its possible mortality and complications, is usually necessary after ileostomy for good results. Today's minimal mortality of approximately 5 to 12 per cent from these three operations, together with the life-long handicap of an ileostomy contraindicates such surgery if medical treatment can control the disease. Until the entire colon, including the anus, is removed, these allergic tissues in many patients will be painful, inflamed, yielding mucus, blood and serous fluid and be susceptible to secondary infections with resultant fever, abscesses and fistulas as long as the causative food and/or inhalant allergies are uncontrolled. Such surgery in our opinion removes the shock organ of allergy, which is impossible in any other manifestation.

With our plan of treatment, fever, diarrhea and bleeding may continue for three to six weeks or even for longer periods with later recovery. The recent use of Aureomycin, Chloramphenicol and Salazopyrin by mouth has controlled infection in some patients, helping to obtain better results with the control of the allergies. If nutrition is being maintained as above advised, and if possible secondary infection and anemia are treated as above described, then prolonged treatment based on food and inhalant allergy as the major causes is highly justifiable. Especially in moderate and uncomplicated cases, surgical treatment is not justifiable. Recovery, moreover, has occurred in a number of our very severe cases in which ileostomy previously had been advised. We confirm Bargen's[5] observation that a contracted, fibrotic colon will function well if the causes of the disease become quiescent or controlled. Bocckus holds that such shortened contracted colons at times may be the result of a spasm and edema rather than an irreversible fibrosis. The surgical drainage of perianal or recent fistulas, of course, is most necessary. More extensive palliative surgery around the anus and especially the removal of hemorrhoids in these patients is unwise because of the reduced resistance of tissues arising from infection and especially from localized allergy. The delayed healing of wounds[12] in certain patients with gastrointestinal allergy is of interest. Exaggeration of symptoms or fulminating activation of potential or quiescent chronic ulcerative colitis at times after proctoscopy and especially after sigmoidoscopy contraindicates them except for necessary diagnosis. Forceful proctoscopy especially with anesthesia is unwise. Auer's[3] report of the onset or an activation of severe allergic inflammation after injury of potentially allergic tissue may explain these bad results from proctoscopy. Injury to the mucosa, moreover, predisposes to abscesses and fistulas in patients whose resistance to secondary infection is impaired.

DISCUSSION OF RESULTS

The results of the writer's therapy, the complicating infections, the

all new bottles, new rubber stoppers, and new needles. After each use, syringes were soaked in concentrated sulfuric acid-dichromate cleaning solution over night. Needles were cleansed with detergent before and after soaking one half hour in a 1 per cent solution of sodium hydroxide

Fig. 4. Forearm of a patient with chronic brucellosis showing hypersensitivity reactions. The old scar in the central area resulted from a diagnostic skin test given four years before. The upper medial reaction resulted from a 10^{-18} dilution of Brucella vaccine given forty-eight hours before. Below it is a smaller reaction to a 10^{-19} dilution. Injections of a 10^{-20} dilution and a control were given equidistantly below these but the sites are scarcely visible after forty-eight hours.

in 75 per cent alcohol. An attempt was made to eliminate every possibility of contamination with unmeasured amounts of Brucella vaccine. Control injections proved that there was no contamination from bottles, stoppers, diluent, phenol, syringes, needles, the alcohol for skin sterilizing, or the cotton applicators. But when the twentieth dilution was injected into Case 4, cited above, she reacted with cutaneous and subcutaneous nodules which remained palpable for three weeks. At the end of this time, two of these nodules were excised and sent to a pathologist for examination. His report was: "Low grade, chronic inflammation in subcutaneous tissue. In the corium is a central area showing an increase in the amount of fibrous connective tissue moderately infiltrated with small round cells."

Figure 4 shows the forearm of another hypersensitive patient who reacted to these extreme dilutions of Brucella vaccine. The upper central portion shows the healed scar of a necrotic reaction to a skin test given four years ago. Medial to it are three intracutaneous injection sites in a vertical line. The lowest one is negative, and is therefore scarcely visible. It was the site of injection of 0.05 c.c. of the twentieth decimal dilution of oxidized Brucella suis vaccine. The middle site, just over the vein, shows the slightly swollen, indurated erythema due to 0.05 c.c. of the nineteenth

TABLE I. CHRONIC ULCERATIVE COLITIS IN 101 CASES STUDIED IN THE LAST ELEVEN YEARS

Hospital Cases: 75 Office Cases: 26 Total: 101

Major Causes in Co-operating Patients (determined by results)

Food allergy	54 cases
Food and pollen allergy	4 cases
Pollen allergy alone	1 case
	59 cases

(In 29 of these 59 cases obtaining good or excellent results, no sulfonamides or antibiotics were used.)

Probable Major Causes in Patients Whose Time of Co-operation was Limited

Food allergy	14 cases
Food and pollen and other inhalant allergies	7 cases
	21 cases

Patients Under Present Treatment	
Probable allergy to foods and/or pollens and inhalants	6 cases
Poor Co-operation Occurred in	5 cases
(No co-operation in 15 cases, not included in this article.)	
Failure from Antiallergic and Medical Treatment	4 cases

OPERATIONS

In five of the above patients previously controlled by antiallergic and medical treatment, ileostomy and later colectomy were done because of severe exacerbations. In our opinion these recurrences were due to breaks in the diet and/or uncontrolled pollen allergy in four patients. Complicating exacerbated infection was responsible in one patient. Ileostomy and colectomy were done in three patients with probable allergic colitis, but in whom we found co-operation was inadequate.

In three other patients who received no antiallergic treatment, ileostomy was done, with two deaths.

DEATHS

In addition to the above two deaths, fatalities occurred in three cases from peritonitis during the first week or two of antiallergic and medical treatment. Death from peritonitis occurred in four patients previously controlled with our treatment. Ileostomy and/or colectomy were done in three of these patients. These deaths from peritonitis occurred before penicillin was available or when its use was restricted, or before streptomycin, Aureomycin, Chloramphenicol and Salazopyrin were discovered.

operations and deaths occurring in all patients studied in the last twelve years are summarized in Table I. As the study has progressed, it has become increasingly evident that good results demand an understanding by the doctor and the patient of the characteristics of clinical atopic allergy and its response to indicated treatment. All physicians treating chronic ulcerative colitis should study these characteristics, progress and response to the treatment of food and inhalant allergies in many cases, especially of atopic eczema or dermatitis, a replica of which in the writer's and Andresen's opinions is the major and underlying pathologic process in chronic ulcerative colitis. The physician moreover must gradually establish a philosophy in the patient which assures unswerving continued co-operation and accepts accurate diet trial and later prolonged elimination of probable or definitely allergenic foods, which justifies eating for health and maintenance of nutrition rather than pleasure alone, and which in inhalant-sensitive patients accepts the careful and necessarily prolonged desensitization therapy and the use of pollen and dust filters and environmental control when indicated. This necessary and restraining philosophy is a small requirement compared with the lifelong handicap and inconvenience of an ileostomy and the usually required total colectomy as the other alternative.

With the realization of the above and the better control of secondary infections with aureomycin, chloromycetin and streptomycin along with penicillin and the sulfonamide drugs, our results in co-operative patients during the last two and a half years have greatly improved, as compared

TABLE I. THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

Patient	Age	Sex	No. Yrs. Asthma	Type of Previous Treatment for Asthma	Results of Previous Treatment	Side Reactions From Previous Treatment	Treatment with Isuprel Sublingual	Oral	Subcutaneous	Reactions
A.P.	24	F	2–3	Ephedrine and Amytal cap. Adrenaline 0.5 to 1 c.c.	No relief Relief in 20 min. with recurrence within 1–3 hrs.	None Palpitation Nervousness Faintness Nausea	5 mg. tab. Relief in 15 min. Recurrence of dyspnea in 2 hrs. 5 mg. Relief in 25 min. Recurrence in 4 hrs.	10 mg. Every 4 hrs. Stopped — not enough relief	Refused	Palpitation Nervousness Palpitation Weakness Nausea
D.M.	14	F	2	Tedral 3 gr. Aminophylline 3½ Adrenaline 0.5 c.c.	Relief 1–2 hrs. Relief 4–6 hrs. Relief in 10 min.	None None Palpitation Weakness Nausea	5 mg. Relief in 10 min. for 1 hr. 5 mg. Relief in 10–20 min. for 1 hr. 5 mg. Relief in 30 min., lasted 30 min.	10 gr. every 4 hrs. Relief in 5 min. No recurrence for 48 hrs. Stopped		Severe palpitation and faintness Palpitation
E.B.	36	M	28	Ephedrine Calc. gluconate Amesie Tedral Adrenaline 1:1000 (1 c.c.)	None None Slight Slight Fair but became adrenaline fast	None Palpitation Faintness Nausea	5 mg. Relief in 10 min., lasting 1–2 hrs. Taking above 2–4x a day	No relief in ½ hr.		None
A.Y.	64	F	15	Aminophylline intramuscularly Tedral Amesie	Relief for 4–5 hrs. Slight Relief in 45 min. for 2–3 hrs.	Dizziness Nausea and vomiting Precordial pain None Slight palpitation	5 mg. Relief in 20 min. 5 mg. Slight relief in 30 min. 5 mg. 45 min. later. Relief for 24 hrs.	60 mg. in 30 hr. No marked relief. Patient stopped treatment of above	Refused	
J.W.	84	M	22	Ephedrine ¾ gr. Adrenaline 1 c.c.	Slight relief with recurrence in 1 hr. Relief	None Severe palpitation. Nausea. Faintness Dizziness	5 mg. Relief in 8 min., lasted 1 hr. 5 mg. Relief in 15 min., lasted 4 hrs. 2–5 mg. tab. at 2 hr. intervals. Relief in 10–20 min.	10 mg. T.I.D., thereafter comfortable	None used	None

with those obtained in the first years of our study and treatment. Up to nine years ago the possibility of pollen and other inhalant allergy often associated with food allergy as a cause of chronic ulcerative colitis was not realized. Since then, its importance gradually has become apparent, as will be reported in a forthcoming article. And the greater frequency of food allergy has been increasingly confirmed. Evidencing this improvement from our treatment is the occurrence of no death, ileostomy or colectomy in any patient who has continued to give full co-operation to the writer during these last two and a half years. But the understanding of the allergic cause and necessary treatment and the accepting co-operating philosophy may not be obtainable, justifying in such unfortunate patients the removal of the shock organ of allergy, the colon, which is impossible in any other manifestation of atopic allergy. This radical operation must be done, hoping that the occasional later establishment of the small intestine as a similar shock organ of allergy, with the development of regional *and usually progressive enteritis, will not occur.*

With the above comments in mind, the writer presents his statistics on all the patients with chronic ulcerative colitis studied during the last twelve years.

In our opinion our results indicate allergy as the major cause in fifty-nine patients in whom co-operation was satisfactory and in another twenty-one patients even though the time of their co-operation was limited.

Of the fifty-nine patients, thirty-eight have continued to co-operate for an average of three and one-fourth years, varying from one-half to eight years. Co-operation in another eleven patients continued for an average of one and one-half years, varying from one-fourth to two years; their present control is not known. Good or excellent control occurred in ten other patients for an average of two and four-fifth years, varying one-half to eight years. Recurrences in these ten patients, in our opinion, were due to breaks in diet in five cases. In two of these, ileostomy and colectomy produced good results. These operations were advised by other physicians and do not exclude the possibility that continued treatment based on the evident allergy with the present control of secondary infections would have yielded good results. Ileostomy, complicated later with perianal abscesses and peritonitis, resulted in death in one patient previously controlled by our treatment for eighteen months. Ileostomy was successful in one patient for six months. Then death resulted two years ago from recurrent ischorectal abscess, peritonitis and ileal obstruction. One patient, controlled with an elimination diet for eight years, developed persistent bleeding and fever, relieved by the removal of a vascularized infected descending colon. The possibility of a complicating pollen allergy during the last two years was present, but co-operation in indicated treatment was not obtained.

The twenty-one patients whose co-operation was limited, but whose results in our opinion indicated food and inhalant allergies as the cause, were under treatment for an average of two and one-half months, varying from

TABLE I. (Concluded)

M.E.	56	F	8	Tedral Aminophylline gr. 3½ Adrenaline .5 to 1 c.c.	None Fair Good	None Nausea and flushing Palpitation Weakness Nausea and vomiting	1st 5 mg. Relief in 15 min. 2nd 5 mg. Improved but not completely relieved	Refused		Severe palpitation and weakness. Refused further medication
J.B.	42	M	2	Ephedrine ⅜ to ¾ gr.	Fair	None	1st 5 mg. Slight relief in 10 to 15 min. 2nd 5 mg. Mod. relief 10–15 min. 3rd 5 mg. No further relief	80 mg. in next 36 hrs. Still slight dyspnea	Refused	None
H.G.H.	48	F	4	Ephedrine ⅜ to ¾ gr. Tedral	None to Slight. Slight	None None	1st 5 mg. stat. Relief in 5 min. 2nd tab. Relief in 5–10 min.			Severe palpitation Palpitation
M.H.	58	F	13	Ephedrine ¾ gr. Tedral Adrenaline	Fair Fair Good for few hrs. only	None Palpitation and faintness	.5 mg. Relief in 10–15 min., lasted 30–40 min. .5 mg. Relief in 10 min. 30–40 min. relief only	10 mg. 4x daily. Slight to fair relief	.15 c.c.	None None Slight
W.L.	11	M	3	Tedral Amodrine Adrenaline .25 to .5 c.c.	Fair Fair Good for 1–3 hrs.	Palpitation and nausea	5 mg. Partial relief, in 8–10 min. for 1 hr. 2nd 5 mg. Relief for 30–60 min.	10 mg. 4x daily. Good relief		Slight palpitation and headache
M.K.	26	M	5	Ephedrine gr. ⅜ Tedral	Fair Fair	None None	.5 mg. Relief in 10–15 min. for 2–3 hrs.	None		Mod. palpitation ½ hr. after tab.
G.H.	38	F	8	Ephedrine Aminophylline intravenous 3¾ gr.	Fair Good	Slight palpitation Flushing Weakness	.5 mg. Good relief in 10 min. for 20 to 40 min. 2nd Relief for 1 hr.	10 mg. 4x daily. Fair relief		Some palpitation after sublingual and oral tab. for 15–40 min.
H.S.	54	F	16	Tedral Amesie Adrenaline .5 to 1 c.c. every 1–2 hours	Poor Good but becoming less effective	None Palpitation and some nausea	.5 mg. No relief in ½ hr. 10 mg. Slight relief in ½ hr.	None	.2 c.c. moderate .4 c.c. complete for 3 hrs.	None
H.S.	73	F	30	Asthmador powder Pyribenzamine	Slight to mod. relief None	None	.5 mg. Relief in 15 min. No further attacks	30 mg. daily		None
M.W.	61	F	20	Cough mixtures?	Slight relief	None	5 mg. Relief in 10–15 min. for sev. hrs.	Not given	Not given	Palpitation Palpitation for ½ hr. after taking.
H.N.	36	M	5	Ephedrine Adrenaline	Slight to mod. relief Complete	Palpitation Palpitation and nausea	5 mg. Slight relief in 10–12 min. 5 mg. Moderate relief. 5 mg. No further relief	60 mg. in 24 hrs. No complete relief	.3	Relief. Palpitation for 10–15 min.

two weeks to eight months. That allergy was the probable major cause was indicated by the rapid control of symptoms, including the diarrhea, blood and mucus in the stools, cramping pain and fever in varying combinations. Sulfa drugs and penicillin were not used in ten of these patients. Penicillin and/or sulfa drugs were used in ten and penicillin alone in one patient. Food allergy was probable in nineteen and questionable in two of these patients. Ileostomy and colectomy in three and ileostomy in one of these patients were done. In these four patients co-operation was insufficient to exclude the possibility of relief from our treatment.

The comments on the operations and deaths in Table I in this series of 101 patients are sufficient. As stated above, it is our opinion that with our present attitude toward treatment and the full use of our new and old antibiotics fewer operations and deaths would have occurred.

CASE REPORTS

Case 1.—In 1942[13] the writer reported the first record of seasonal chronic ulcerative colitis of eight years duration, relieved by pollen therapy.

The woman, aged forty-eight years, was first seen in the Allergy Clinic at the University of California Hospital in September, 1940. Watery or loose stools with blood and mucus, associated with moderate varying fever, weakness, malaise and dull cramping pains in the lower abdomen, had recurred each year since 1931 from July or August until late November or December. Proctoscopic examination in 1934 in this clinic and since then in the fall months had revealed a granular, hyperemic mucosa with many ulcerations and bleeding areas. In 1936 a vaccine from the stools of hemolytic bacillus coli, staphylococcus aureus and alpha hemolytic streptococcus was given subcutaneously. The lysate was applied to the rectal mucosa and a phage from the bacteria was given by mouth. No relief was obtained.

Sick headaches had long recurred with her periods. Mild hay fever had occurred from 1918 to 1923 in Chicago. Her dietary history was negative except for belching fresh eggs. Her family history was unknown.

Skin testing with all important food and inhalant allergens by the scratch and intradermal methods was negative except for 1-plus reactions to red top and curly-lock pollens. Negative reactions occurred to her allergenic fall pollens.

Since her relief reported in 1942 from pollen therapy, perennial desensitization has continued with a multiple pollen antigen with complete control of her former symptoms of chronic ulcerative colitis except for a few loose stools for a week or so in the spring of 1943 and the fall of 1946. No consideration of food allergy and no other medication of any type has been given during this eight-year period. As previously reported, her eosinophilic leukocytes when first seen were 22 per cent. In four months they were 6 per cent, and in three more months when the pollens were out of the air they were 1 per cent.

Case 2.—Mrs. W., aged thirty, was first seen in the Peralta Hospital, because of chronic ulcerative colitis in January, 1944. Since the fifth month of pregnancy five years previously, two to twenty liquid stools with frequent traces of blood had been passed each day. Lower abdominal soreness and nearly constant tenesmus and urgency with movements had necessitated immediate access to the bathroom. Slight fever had been present and marked physical weakness, irritability and nervousness had occurred. Her weight had fallen from 165 to 135 pounds.

There had been no previous gastrointestinal symptoms, except for varying degrees of constipation for many years. There was no history of any previous chronic or allergic disease.

and asthma. Reactions characterized by jaundice, acute yellow atrophy of the liver, and optic atrophy are probably not allergic. Those with granulocytopenia, anemia, thrombocytopenia, and polyneuritis may or may not be allergic. (b) Allergy seems present if a primary or sensitizing administration of a drug appears important in the history; if drugs are long-continued or large in amounts the factor of allergy is unlikely. (c) An allergic basis is probable if relief of symptoms follows epinephrine, Benadryl or similar agents. But allergy is less likely if relief occurs after such therapy as ascorbic acid, folic acid, thiamine, or other agents whose good effects are not anti-allergic. Sherman[167] also discusses allergy to drugs, especially to tragacanth used to coat pills.

Salen and Arner[139] say aspirin allergy is the most frequent form of drug allergy, and occurs in about 8 per cent of all their asthmatic patients and twice as often in those with severe asthma. Death may occur from small doses; therefore patients and nurses should be warned. They also point out that "there are lower degrees of aspirin allergy in which the drug in normal doses only gradually—perhaps only after one to several days' medication—causes a perceptible exacerbation of the asthma, which subsides only when the drug is discontinued." Patients with aspirin-sensitivity are not more severe than the average case, despite previous reports by Van Leeuwen, Feinberg and Prickman. Prickman and Morgan[396] cite five more cases of sensitivity to aspirin, with asthma and nasal polyps, a triad frequently noted and usually associated with severe asthma and a poor prognosis (thus differing from the previous observers' opinion). In addition, there were twelve cases of drug intolerance of which four were to morphine (nausea, vomiting and in one case coma with marked asthma), and others to iodized oil, bromides, iodides and phenobarbital.

Reactions to drugs are very numerous, often with urticaria and/or dermatitis, but asthma may result as in the following case reports. Thiamine caused severe itching, inflammation, asthma and collapse, with recovery after epinephrine; this patient of Shapero and Gwinner[165] gave positive scratch and intradermal reactions with dilutions as low as 1 mg. per c.c. (controls gave positives only with dilutions of 25 and 50 mgs. per c.c.). Fineberg[184] reports two cases apparently due to nicotinic acid. In one of these substernal tightness, burning, tachycardia, cardiac irregularity and prostration occurred after the sixth intravenous injection of 150 mgs. Relief followed a little epinephrine. Skin tests with 1 per cent nicotinic acid were positive in one case, negative in the other. Barnett[51] reported four deaths, three with autopsies, after the use of "Analbis" suppositories, a bismuth compound said to be effective in upper respiratory infections and said to be non-toxic. One boy aged six, with asthma, received daily suppositories for three weeks, none for four days, then four in 48 hours for pharyngitis. On the fifth day the pharyngitis subsided, tonsils were removed (ether), and coma and death occurred thirty-six hours later. In this case and in the other two autopsies cerebral edema and fatty liver were found. These suppositories have been withdrawn from the market and are being studied.

A fifteen-year-old patient of Whittemore and DeGara[557] was given 0.5 gm. sulfadiazine for recurrent furunculosis. Within ten minutes there occurred cough, itching thighs, flushed face, and wheezing, and in five minutes symptoms of suffocation with marked hoarseness and unintelligible speech, also large wheals. This girl had received this drug about three weeks previously. Relief was obtained with Adrenalin. There was also a history of previous asthma. Scratch tests were strongly positive with sulfadiazine and much larger with sodium sulfadiazine, and also with thiazole. Passive transfer was positive with diazine and thiazole (control negative), and this phenomenon was also positive ten days, twenty-five days and seven months later—all this proving the sulfadiazine sensitivity. Tests for other sulfa drugs were negative. Frouchtman,[205] from Barcelona, had an asthmatic patient with infected tonsils. Sulfathiazole seemed to aggravate her asthma. As a test a small quantity of this drug was blown into the patient's nostrils, with resultant severe asthma, followed by collapse. Later, the ingestion of the same product (Cibazol) did not produce immediate effects but that night the patient had some dyspnea. Intradermal and passive transfer tests were positive with this drug. Penicillin rarely causes asthma but Kohn's[286] two-year-old boy received three intramuscular injections, each 300,000 units; six days later the child developed severe asthma, with relief by epinephrine. [This patient received sulfadiazine for four days before penicillin was started; perhaps the asthma here was a delayed sulfa reaction?]

A nurse with dermatitis was tested with 0.05 c.c. stock solution of streptomycin. Within two minutes a severe constitutional reaction occurred, with generalized itching, wheezing, abdominal cramps, and collapse. Fortunately, she was revived by epinephrine and Pyribenzamine. She had never had previous injections of

Proctoscopic and roentgen ray studies of the colon on three occasions had confirmed the present diagnosis. In spite of treatment from several internists, relief had failed. Recently her disease had been attributed to a repressed abnormal sexual desire of late childhood!

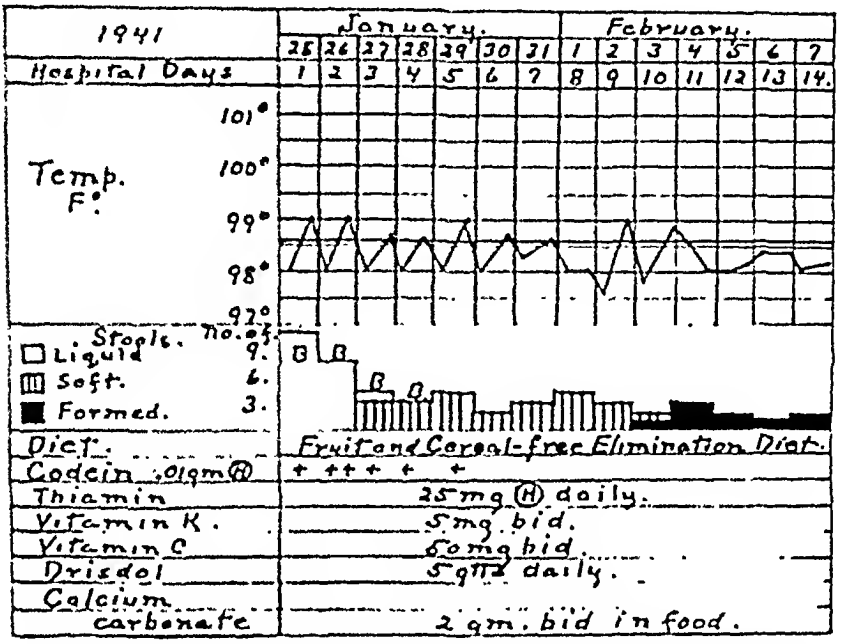

Fig. 1. *Case 2.* Mrs. F. W., aged thirty. Chronic perennial ulcerative colitis controlled with the fruit and cereal free elimination diet without sulfonamides, penicillin or other drugs. The diarrhea, blood in the stools, cramping and slight fever gradually disappeared in the first ten days of the diet, and soft, less frequent stools appeared in three days. As in Case 3, this colitis developed during pregnancy. Excellent control for eight years has required the elimination of allergenic foods as noted in the case record.

Her dietary, drug and environmental histories revealed no indication of allergy. Likewise her family history was negative for allergic and chronic illnesses.

Her physical examination revealed a fairly well-nourished woman complaining of lower abdominal soreness, cramping and passing of numerous watery, bloody and mucoid stools. There was tenderness on pressure over the entire colon, especially in the lower left quadrant. Her blood pressure was 110/70. The rest of her examination was negative.

Laboratory Studies.—Urinalysis was negative. Hemoglobin was 73 per cent, leukocytes 9,400—polymorphonuclear cells 75 per cent, with 50 per cent segmented forms, lymphocytes 16 per cent, large mononuclear cells 7 per cent. Stools examined for ova and parasites were negative.

Roentgen ray study of her colon revealed marked shortening throughout with a tube-like, nonhaustrated appearance. Diffuse destruction of the mucosa was evident. Multiple constrictions were seen in the rectosigmoid and transverse areas, and to a lesser extent in the descending colon. The ileocecal valve was wide open and the terminal ileum was slightly distended.

Conclusion.—Extensive chronic ulcerative colitis of the entire colon.

Skin testing with all important food and inhalant allergens gave no reactions by the scratch method.

Treatment and Progress.—The writer's fruit and cereal-free elimination diet, vitamin C and calcium carbonate, as shown in Figure 1, were ordered. Vegetables

and emphysema; in the latter group the resting pulmonary pressure, with one exception, was higher than in the normal. On exercise, pressures in the pulmonary arteries increased still more beyond the normal range. This was expected because of the narrowing of pulmonary vascular channels in emphysema.

Riley and his co-workers[117] also catheterized the pulmonary arteries of three normal persons and eight patients with various types of chronic pulmonary diseases including bronchiectasis and emphysema. In two of the three normals a fall in mean pulmonary artery pressure occurred during exercise (a slight rise in the third). On exercise all three showed a marked drop in pulmonary vascular resistance and a minimum increase in work of the right ventricle. On the other hand, three of the eight patients at rest showed an elevation of pulmonary artery pressure and all developed increased mean pressure during exercise. The pulmonary vascular pressure remained stationary or was increased at the same time, and the work of the right ventricle was always greater in these patients than in normal persons at the same work level. In patients with chronic heart disease the rise in pulmonary arterial pressure with exercise is due to decrease of arterial oxyhemoglobin saturation and increased pulmonary resistance resulting from lung tissue destruction, interstitial pulmonary fibrosis, or vascular sclerosis.

Gray and Green[228] have a fine article on the voluntary ventilation capacity in normal individuals. They have standardized the procedure so that it is a very useful clinical test of the functional capacity of the respiratory tract. They point out that the "ventilatory capacity may be measured as the maximum possible respiratory minute-volume. Ventilatory capacity in this sense depends upon two primary factors, the functioning lung volume (vital capacity) and the dynamic flow of air through the respiratory passages. These two factors may be affected *independently;* there *may* be reduction in the vital capacity with little change in resistance to the flow of air, as in pneumothorax, or there may be increased resistance to the flow of air with little change in vital capacity, as in bronchial asthma. As a result the vital capacity alone is *not* a measure of ventilation capacity. Unfortunately, it has been commonly interpreted as a measure of ventilation capacity but this interpretation is clearly fallacious."

Using a modification of a standard Benedict-Roth spirometer the individual is instructed: "This is a test to determine how much air you can breathe in and out of your lungs in twenty seconds when you breathe just as hard as you possibly can. In order to move the most air, you mustn't concentrate on breathing only fast, or only deep, but instead you must compromise between the two in such a way as to maintain the most rapid flow of air in and out of your lungs." In eighty-nine aviation students the reliability coefficient of the test was 0.90. The mean ventilation capacity was 168 liters per minute, with a standard deviation of twenty-two liters per minute. The ventilation capacity was found to be correlated with surface area, but not with age, height or weight. [This method is obviously much more accurate than is the simple, vital capacity technique which most of us have used in the past. An asthmatic patient may be able to take one deep inspiration and expiration, and his vital capacity as judged from this one respiratory act may well be 50 to 75 per cent of normal. But this same patient's ventilatory capacity will have a much lower percentage than normal, perhaps only 5 to 10 per cent, because he simply cannot breathe deeply and rapidly over a period of twenty seconds as required by the new test. The test therefore fits in with clinical experience, e.g. dyspnea on such exertion as climbing one flight of stairs, much better than does the vital capacity test. The test is simple and very much worth while.]

Tuft, Blumstein and Heck[517] also review the physiology of the lung with particular attention to external and internal respirations and the circulatory status. They agree with the previous authors. Their patients are asked to breathe rapidly and forcefully for thirty seconds, and their "maximum breathing capacity" (B.R.) is similar to the ventilatory capacity previously described. The B.R. corresponded to the clinical degree of asthma in all twenty-two cases, all of whom had more or less emphysema. They also estimated the B.R. before and after giving 0.50 c.c. epinephrine. In those whose B.R. remained low even after epinephrine there was also a clinical low tolerance for exertion—this invariably due to pulmonary fibrosis or emphysema, either resulting from or associated with the asthma. The absolute functional pulmonary impairment can only be determined after elimination of as much bronchoconstriction as possible by such a bronchodilator as epinephrine. The degree of disability invariably parallels the results of this dynamic type of spirometry and will not necessarily bear a constant relationship to the changes in the size or shape of the chest.

Jiménez-Díaz and his co-workers[271] describe their experimental arrangements and show that differences in the filling with blood of the smaller circle are accompanied by parallel differences in the air volume and rigidity of the lung. As an increase

were pureed. Extra sugar was given in the form of cane syrup, in carbonate water and tea, in order to increase calories. Codeine was administered to relieve the severe abdominal cramping during the first few days.

Bowel movements reduced from eleven to four, and from liquid to soft in three days, and one to two formed movements were present after the tenth day. Abdominal soreness and cramping stopped on the sixth day, and her slight fever disappeared on the eleventh day.

In the last eight years there has been no return of diarrhea, bleeding, cramping or urgency with bowel movements. One or two formed daily stools or intermittent constipation have occurred. She had led a normal daily routine, doing her own house work, visiting friends and shopping, riding on horseback and in automobiles without fear of urgent bowel movements.

To maintain this control she has continued to eliminate all milk and its products, tomatoes, cabbage, cauliflower, eggplant, citrus fruits and spices. She has limited her intake of eggs and wheat.

"My colitis is very well controlled, though with carelessness with diet evidences of it return. It never restricts my activity. I am happy to be doing all the things I wish, especially in the last six years. In the summer and fall months for the last three years we have gone to a horse show every weekend. I can ride 10 to 20 miles a day without symptoms and without fatigue the next day. My present weight is 142 pounds."

Comment.—The rapid relief of this diarrhea with varying amounts of blood and mucus and the daily cramping, tenesmus and bowel urgency, and her return to normal family and social routine without fear of sudden bowel movements depended entirely on the prescribed elimination diet. As in twenty-eight other patients obtaining good results in this series, no sulfa drugs or antibiotics were given.

In this patient the colon was the only shock organ of allergy. The dietary history, as so often occurs, revealed no dislikes or idiosyncrasies for any foods suggestive of possible allergy. The skin reactions were negative as was the family history for allergy. Constipation, as in Case 3, for a number of years was the only preceding gastrointestinal symptom.

During the last five years slight indications of her former colitis have occurred for only a day or two when small amounts of milk and other foods listed above have been eaten against orders. She has led a normal, vigorous and happy life, realizing the necessity of adhering to her elimination diet.

Case 3.—A woman, S. S., of thirty-nine years, was first seen in the University of California Hospital in October, 1945, because of chronic ulcerative colitis. Diarrhea had developed in the seventh week of her third pregnancy three years previously. Mucous colitis was diagnosed, but diet and medications were ineffectual. Since then, seven to eight soft or liquid stools had been present practically every day. In January, 1944, treatment in the hospital gave no relief. Stool examinations for parasites and pathogenic bacteria were negative. During these three years stools had become more watery, foul and bloody. Great urgency had been present all the time, requiring constant proximity to the bathroom. Because of economic necessity she had done some housework every day, even though moderate weakness and a loss of 10 pounds had occurred. Diet, medicines and other treatments had failed. Moderate fever had occurred at intervals and had been present for the last two weeks.

Except for constipation throughout her life, no other symptoms or illnesses had ever occurred before this illness.

Her dietary history revealed no dislikes or idiosyncrasies for any foods.

Her environmental and drug histories revealed no indication of possible allergy.

Her family history also was negative for chronic disease and allergy.

THE TREATMENT OF BRONCHIAL ASTHMA

Specific treatment continues to be neglected. Perhaps we have reached the stage in which specific avoidance, with or without hyposensitization, is accepted as the best treatment for patients with bronchial asthma. But we doubt the correction of this assumption. Some of us, we hope the majority, still try to find the cause of attacks and to remove or combat in a specific manner. But many physicians, including a few allergists, have become so interested in the newer drugs that they have not clung to the narrow but most fruitful measures, those which are specific and which undoubtedly give the best results. All other measures—and they are legion—can only give temporary improvement. The new agents must not be neglected—some are valuable, but they must not supplant those which have been successful.

Branderberg and Wilander,[80] from Sweden, discuss desensitization in twenty-eight allergic children, chiefly asthmatic. They obtained better results with extracts prepared from surroundings close to the patient. They made some extracts which seem unusual to us, e.g. birch leaves and catkins, hazelnuts, boiled and raw milk, cooked and raw egg yolk and egg white, and sawdust. Injections are raised till the child tolerates 1.0 c.c. of the undiluted extract; they usually reach this dosage in eight to fourteen days and then the injections are repeated monthly for one year. No deaths occurred. Sixty per cent gave positive skin tests to house dust, and about one-third to horse, cat and/or cattle danders. The results were excellent in nineteen (76 per cent) of twenty-five patients and poor in six (24 per cent). There were no complete recoveries. One child developed angioneurotic edema to fish and horse dander extracts but persistent injections once a month led to good results. The authors are favorably impressed by this specific hyposensitization and urge its use before the condition becomes chronic. Glaser,[223] commenting, says this method of treatment is "at such variance with the common experience in this country. Hypodermic desensitization is almost never practiced to foods in this country. The feeling among pediatricians, and this is commonly borne out by experience, is that if the child refrains from eating a particular food, he will eventually, even though it may take several years, lose his sensitivity to that particular food. Hyposensitization to foods by the method of injection is considered extremely dangerous and exceedingly time consuming, and scarcely worth the risk and effort."

[We agree with Glaser that allergy to foods diminishes with avoidance, and that hyposensitization to these foods by the hypodermic method is rarely necessary. But Glaser did not mean that avoidance will eventually bring loss of sensitivity to all foods. Those who are highly allergic to fish, eggs, or nuts almost certainly remain sensitive to those foods. Hyposensitization (oral or hypodermic) will lessen the sensitivity in most patients, and is no more dangerous than with such a potent allergen as horse dander. We have given injections of egg white extract to many children because of extreme sensitivity to egg, and have been rewarded by an increase in tolerance to the point where the patient can eat egg-containing foods or even a little cooked egg. We also inject wheat-sensitive patients; they obtain results much more quickly unless their exposure is overwhelming. We do not give injections of any other food extracts as these other foods are not essential. We would hyposensitize for milk if we could find or make a good extract.]

Henriksen[253] made a follow-up study of 100 asthmatic patients who had received specific desensitization three years previously. Remarkable improvement was still present in 59 per cent, but 16 per cent of these claimed that factors other than desensitization caused the improvement. The final figure is therefore 43 per cent.

TREATMENT OF ASTHMA BY DRUGS

Rackemann[403] has such an excellent editorial that we quote it in full. He says:

"Many interesting ideas and many 'good' experiments have been 'spoiled' by controls. How easy it is to believe that when a result follows a procedure that this result always depends upon that procedure. Propter hoc is very different from post hoc. In asthma, indeed in all the allergic diseases, the danger is greater than usual. This is not only because the nature and cause of the process is still obscure, but particularly because so many different factors can play their parts in it.

"New methods of treatment are particularly open to the risk of a hasty belief in their benefit. We recall our enthusiasm when ephedrine first appeared. Aminophyllin was hailed next. Histamine, given by itself or later in protein combinations, was recommended warmly as a panacea. Now, however, we have learned of its limitations. During this past year or two the antihistamine drugs have been described, extolled, and finally relegated to their proper places. New preparations impress the doctor and they impress the patient. Incidentally, a new doctor means a fresh start and a new hope. Almost every new patient reports his asthma improved during the

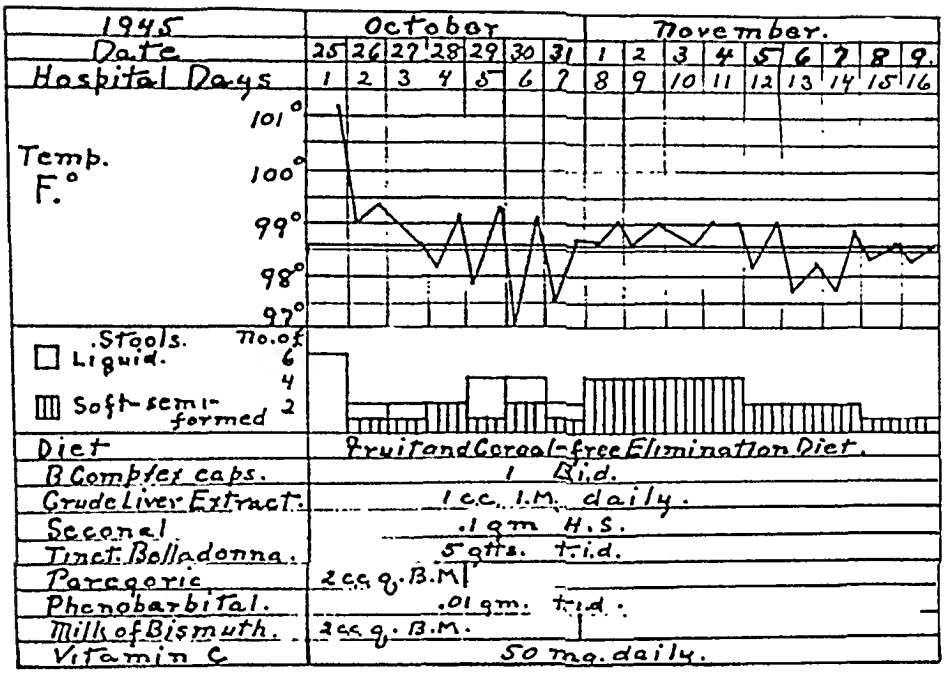

Fig. 2. *Case 5.* Mrs. S. S., aged thirty-nine. Chronic perennial ulcerative colitis controlled by the fruit-free elimination diet. The diarrhea was reduced in one day and to one to two soft stools in twelve to sixteen days. Fever disappeared in thirteen days. No sulfonamides or antibiotics were used. The value of the liver extract and phenobarbital is questionable. In the last three and one-half years two moderate exacerbations due to breaks in the elimination diet have occurred.

Her physical examination revealed a slender, worn appearing, but composed woman, with a temperature of 101° F. Her examination was negative except for moderate diffuse abdominal tenderness and a tender inflamed anus.

Laboratory Studies.—Urinalysis was negative. Blood count (October 25) showed hemoglobin 90 per cent, erythrocytes 4,700,000, leukocytes 8,800; differential count showed polymorphonuclear cells 41 per cent, with 30 per cent segmented forms, lymphocytes 43 per cent, eosinophiles 16 per cent. On November 5 hemoglobin was 88 per cent, erythrocytes 4,700,000, leukocytes 8,700; the differential count showed polymorphonuclear cells 73 per cent, with 62 per cent segmented forms, lymphocytes 14 per cent, eosinophiles 14 per cent. Three stool examinations and cultures were negative for bacilli in the typhoid, paratyphoid and dysentery groups. Four stool examinations showed no parasites or ova. Serum protein: albumin 3.2 gm. per cent, globulin 3.9 gm. per cent.

Proctoscopic examination up to 13 cm. showed a granular appearing, erythematous, easily bleeding mucosa. Roentgen ray study of the colon showed a rapid passage of barium throughout the colon which was narrow and rigid. The barium passed into the terminal ileum with little pressure. The borders of the terminal ileum were smooth and rigid. Haustrations in the colon were absent except in a small portion of the ascending colon, and the borders were smooth throughout. Opinion: Chronic ulcerative colitis, probably involving the terminal ileum.

Treatment and Progress.—The writer's cereal and fruit-free elimination diet with other medications shown in the chart were ordered. Fever decreased in the first six days. Soft infrequent stools immediately developed, except for two or three watery stools on the fifth to the seventh days. In one week urgency was less frequent. On discharge on the sixteenth day her fever was absent, urgency had disappeared, and one formed daily stool was being passed (Fig. 2).

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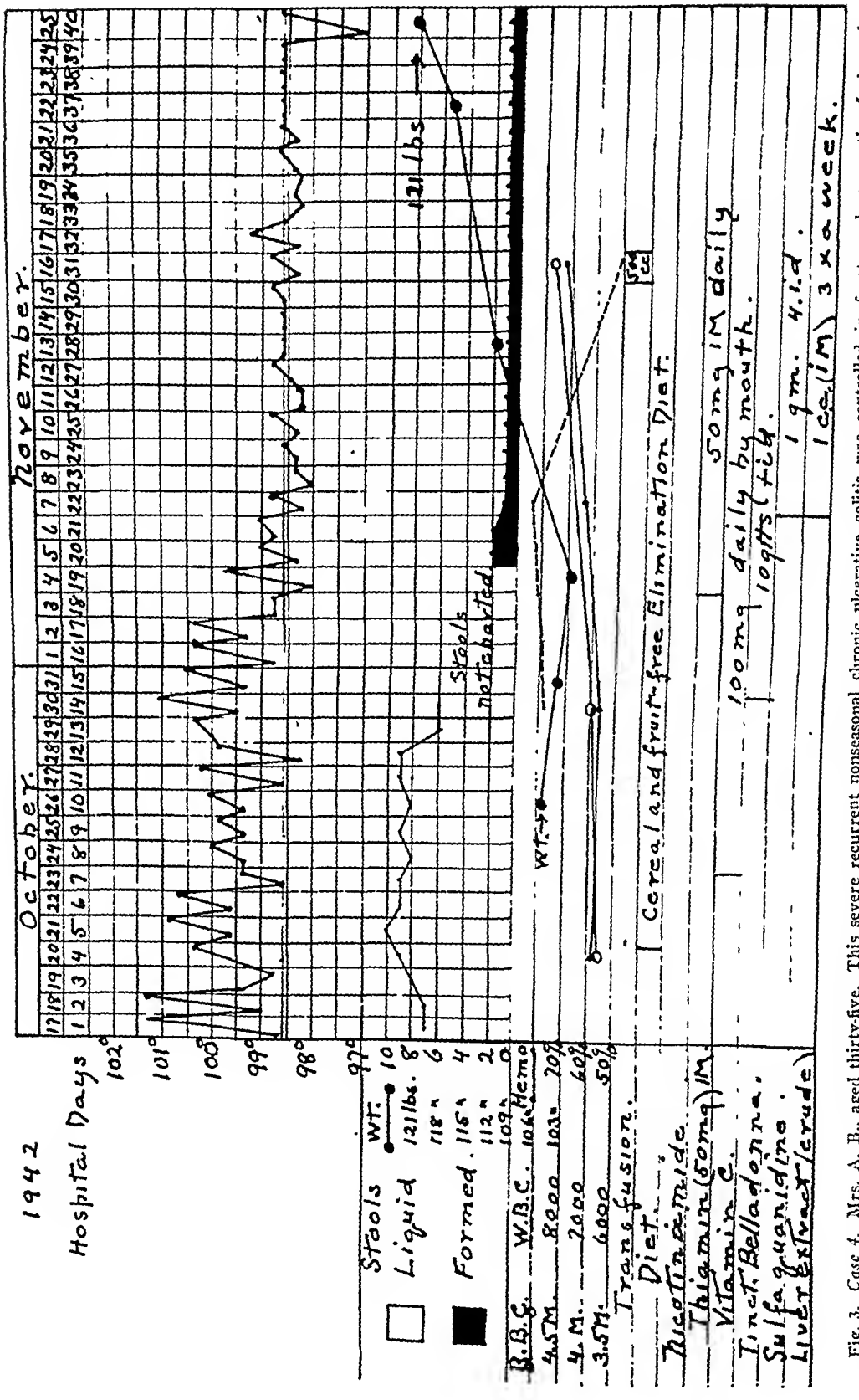

Fig. 3. *Case 4.* Mrs. A. B., aged thirty-five. This severe recurrent nonseasonal chronic ulcerative colitis was controlled in fourteen days on the fruit and cereal-free elimination diet. No sulfonamide or liver extract was given until control of colitis had occurred. As in Case 5, excellent gain in weight resulted with the control of the colitis on this diet, showing that milk and egg are not required, providing the prescribed diet contains adequate calories, protein and vitamins. During the last six and one-half years, there have been three moderate exacerbations of her colitis due to breaks in the diet.

resistant to local oil therapy, twenty-four responded to combined autoserotherapy. These results are superior to those of trichophytin. In using autogenous serum, I feel that we are dealing with species specific antigens which produce homologous antibody. Autoserum is the treatment of choice in stubborn mycotic lesions.

Acknowledgment is made for the laboratory testing of whale oil and the various strains of fungi tested. This work was performed by Dr. Eugene R. L. Gaughran of Rutgers University Department of Bacteriology in 1947.

REFERENCES

1. Andrews: Diseases of the Skin. 3rd ed. Philadelphia: W. B. Saunders, 1946.
2. Beekjord, B.: Prophylaxis and treatment of epidermophytosis. Mil. Surgeon, (Dec.) 1941.
3. Bloch, B.: Allgeneine und experimentelle Biologie der duch Hyphomyceten erzeugten Dermatomykosen. Handb. d. Haut. u. Geschlechtskr., 11:300, 1928.
4. Burlingame, E. M., and Reddish, G. F.: Laboratory methods for testing fungicides used in treatment of epidermophytosis. J. Lab. & Clin. Med., 24:765, 1939.
5. Dimond, N. S., and Thomsom, K. W.: Effect of sulfonamide drugs on trichophytins in vitro. J. Invest. Dermat., 5:397, (Dec.) 1942.
6. Dodge, Carroll: Clinical Mycology St. Louis: C. V. Mosby Co., 1935.
7. Elsdon, G. D.: Edible Oils and Fats. New York: D. Van Nostrand Co., 1926.
8. Henrici, A. T.: Proc. Internat. Cong. Microbiol., p. 567, 1940.
9. Hopkins, J. D., et al: Treatment and prevention of dermatophytosis and related conditions. Bull. U. S. Army M. Dept., No. 77, (June) 1944.
10. Jessner, M., and Hoffman, H.: Der Einfluss des Serums Allergischer auf Trichophytonpilze. Arch. f. Dermat. u. Syph., 145:187, 1924.
11. Keeney, E. L., and Brayles, E. N.: Sodium propionate in the treatment of superficial fungous infections. Bull. Johns Hopkins Hosp., 73:479 (Dec.) 1943.
12. Keeney, E. L., et al: Sodium caprylate, a new effective treatment for dermatophytosis of the feet. Bull Johns Hopkins Hosp., 77:422, (Dec.) 1945.
13. Lewkowitsch and Warburton: Chemical Technology and Analysis of Oils, Fats. Vol. 11. New York: Macmillan, 1922.
14. Martenstein, H.: Arch. f. Dermat. u. Syph., 142:279, 1923.
15. Martin, George: Animal and Vegetable Oils, Fats, and Waxes. New York Appleton, 1920.
16. National Research Council: Manual of Clinical Mycology; Military Medical Manuals. Philadelphia: W. B. Saunders, 1944.
17. Peck, S. M.; Glick, A., and Weissbard, E.: Trichophytin; apparent separation of skin reactive factor from therapeutic principle in trichophytin. Arch Dermat. & Syph., 44:816, (Nov.) 1941.
18. Rattner, B.: Allergy, Anaphylaxis, and Immunotherapy. Baltimore: Williams & Wilkins, 1943.
19. Ruehle, G. L. A., and Brewer, C. M.: U. S. Food and Drug Administration method of testing antiseptics and disinfectants U. S Dept Agriculture, Circular 198, (Dec.) 1931.
20. Shapiro, A. L., and Rothman S.: Undecylenic acid in the treatment of dermatophytosis. Arch. Dermat. & Syph., 52:106, 1945.
21. Sulzberger, M. B., and Kerr, P. S.: Trichophytin hypersensitiveness of urticarial type, with circulating antibodies and passive transfer. J. Allergy, 2:11, (Nov.) 1930.
22. Tomlinson, W. J.: Trichophytin hypersensitiveness; report of case with immediate or reaginogenic type of reaction. J. Allergy, 6:573, (Sept.) 1935.
23. Urbach, E., and Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1946.

In two months strength and appetite had increased and two or three formed stools were occurring daily. In four months there were two to three semi-formed, soft daily stools with no blood or mucus. No gas, cramping or any gastrointestinal distress was present.

During the summer and fall of 1946 all symptoms were controlled. She passed zero to three semi-formed or formed stools daily. Her weight was 100 pounds. B complex capsules daily for one week resulted in diarrhea, and when taken a few weeks later again caused immediate diarrhea.

In December after she had eaten white bread without permission for four days, loose stools developed and increased to eight or nine a day four days later. Soreness and cramping in the right abdomen persisted for twelve days; fever arose up to 100° F. and continued for about six weeks. Five to ten soft to loose bowel movements were passed each day and traces of blood were present in the stools. In mid-February these symptoms gradually disappeared. In two months her weight had increased to 97 pounds. Her appetite was "wonderful," and she felt better than at any previous time in her life. During the fall of 1947 she traveled through the Midwest and occasionally broke her diet. Moderate diarrhea with traces of blood, slight fever and loss of weight resulted. With strict adherence to the diet these symptoms disappeared in two or three weeks.

During the last two years she has adhered to her diet at all times. Her colitis has been well controlled. She has done all of her own work.

Comment. The relief of the long standing diarrhea, cramping, urgency and intermittent fever in two weeks, with continued control in the last four years, has depended on strict adherence to the fruit and cereal-free elimination diet. Only two moderate exacerbations have occurred, both due to breaks in the prescribed diet. In the last two years all of her symptoms have been continuously controlled due to strict adherence to the diet, and no medications of any type have been given. Her health and strength and weight have been normal.

This ulcerative colitis started quite suddenly, as occurs not infrequently in this disease. Constipation present since childhood, as in Case 2, was her only preceding symptom or illness. The absence of a history of dislikes or disagreements for any foods shows that such a history is not necessarily present when allergy to specific foods exists.

Case 4.—A colored woman, aged thirty-five years, Mrs. B., was first seen in the Alameda County Hospital in October, 1942, because of chronic ulcerative colitis. In the preceding one and a half years exaggerated symptoms had been present on three occasions, producing fifteen to twenty-five watery movements, associated with varying amounts of blood and mucus, persistent fever and vomiting two or three times on many days, each attack lasting four to five weeks. Marked weakness, abdominal soreness, tenesmus and cramping and the loss of 15 to 20 pounds had occurred. Between the attacks three to four soft or liquid movements with some mucus had been present each day. The present attack had occurred for four weeks before entrance to the hospital. There was no previous history of gastrointestinal symptoms, chronic or allergic disease.

Her dietary history revealed no dislike or disagreement for foods, though milk "soured" in her stomach during the attacks. Her drug and environmental histories revealed no suggestion of allergy.

Family history revealed severe bronchial asthma in a sister. Her physical examination was negative except for diffuse soreness on palpation over the lower abdomen.

Laboratory Studies.—Her blood count is shown on the chart. Differential count October 17 showed polymorphonuclears 62 per cent, with 26 per cent segmented

forms, lymphocytes 29 per cent, large monocytes 16 per cent, eosinophiles 3 per cent, Wassermann reaction negative. Stomach analysis was normal, plasma proteins (November 19) were 6.5 gm. per cent. Three stool examinations for ova and parasites were negative.

Barium enema revealed absence of normal haustrations throughout the entire colon, especially marked in the descending portion. Conclusion: chronic ulcerative colitis with probable involvement of the terminal ileum.

Proctoscopic examination showed a pale, edematous mucosa with no visable ulcerations.

Treatment and Progress.—With the writer's fruit-free elimination diet, containing a small amount of the prescribed pureed vegetables, decrease in cramping, abdominal soreness and the number of stools occurred in one week, and formed stools were passed in twelve days.

During the next three years her symptoms were well controlled with the continued elimination of milk, wheat and fruit from the diet. All vegetables were taken nonpureed. In July, 1945, she reported three to four watery bowel movements with some epigastric pain and recent vomiting. Cream and uncooked fruit had been taken at times for three previous months. With their elimination her colitis disappeared, and six months later she was well controlled except for one to two soft movements for one day every week or two.

In October, 1947, she reported satisfactory control of her colitis during the preceding year and one-half. One semiformed daily stool had been passed. Recently occasional slight lower abdominal pain had occurred before a movement. Slight errors in the diet had been made, including some milk in cooking and the occasional eating of white bread and tomato. For two or three months she had been fatigued. With the resumption of the strict diet her fatigue and abdominal distress disappeared at the end of one month's time. Ferrous sulfate, 3 grains, three times daily was ordered because of a hemoglobin of 66 per cent. Because of a metabolic rate of minus 16 per cent, ½ grain of thyroid was ordered.

During the last two years and a half her colitis was well controlled until eight months ago. Then for three months abdominal soreness, occasional soft or liquid stools and weakness and nervousness had been present. During the preceding months constant breaks in the diet had been made. With the resumption of her fruit-free elimination diet her symptoms were controlled at the end of two weeks.

Comment.—The rapid control of the diarrhea and the blood, mucus, cramping, tenesmus and fever with the sole use of the fruit and cereal-free elimination diet, as shown in Figure 3, favors food allergy as the cause of this chronic ulcerative colitis. This is confirmed by the continued relief except for moderate symptoms when milk and other forbidden foods had been taken for varying periods in 1945, 1947 and 1948. With the resumption of the strict diet, rapid control of the resultant symptoms have occurred on each occasion. During these last seven years her colitis has not required even a brief hospital residence.

As in Case 1, no sulfa drugs or antibiotics were given while the fever and diarrhea were being controlled. Liver extract and sulfa quanidine were given in the last eighteen hospital days, but in the writer's opinion they were unnecessary.

The gain of weight of 14 pounds in twenty days shows that milk, egg and cereals are not required to increase weight when the allergic causes of chronic ulcerative colitis are controlled. Calories up to 2500 or more and protein up to 100 grams or more each day are readily available even with the minimal elimination diets, especially when the strained meats of Gerber or Swift are utilized.

Case 5.—A woman, Mrs. G., aged thirty years, was first seen in the San Francisco County Hospital in February, 1946, because of chronic ulcerative colitis.

Eight months previously two to three loose daily bowel movements had devel-

oped. During the next two months a gradual increase to ten or twelve watery movements, associated with chills, fever, soreness in the abdomen, cramping and tenesmus and a loss of 20 pounds, occurred. In late August she was hospitalized, and with a milk-free, low residue diet, started after the twentieth day, her fever was reduced from 101° to 99° in thirty-five days. At that time occasional soft stools developed, and at the end of sixty days a normal temperature was present and two to three formed daily stools were passed During her hospital stay three transfusions, B complex vitamins and antispasmodics were given. Sulfasuxidine, 5 grams, four times a day, was given for three weeks after September 8, and crude liver extract, 2 c c. intramuscularly daily, was given for six weeks after September 8

After discharge from the hospital on October 31, milk was added to the diet, and during the next month a normal diet was resumed. Within one month mucus and blood recurred, and in two months she was passing ten to twelve liquid bowel movements, with much soreness and pain in the anus, marked tenesmus, daily fever and a rapid loss of weight.

There was no previous history of any gastrointestinal or chronic illness before the onset of her present colitis Her family history revealed no predisposition to any chronic or allergic disease Her dietary, drug and environmental histories revealed no suggestion of any allergy.

Because of the severe return of her ulcerative colitis since early December, she re-entered the hospital on January 30, 1946 Physical examination revealed a thin, moderately weak woman, weighing 89 pounds, with a temperature of 103° F. Her examination was negative except for moderate distention and soreness on pressure over the lower abdomen. Her blood pressure was 117/70. Sigmoidoscopy revealed an erythematous, granular mucosa which bled on the slightest pressure. Moderate sized ulcers, covered with a purulent exudate, were present in the rectum and sigmoid.

X-ray of the colon revealed a shaggy, saw-tooth outline from the cecum to the lower sigmoid. Marked thickening of the walls was present in the transverse colon Almost a complete loss of normal mucosal pattern was seen from the mid transverse to the rectum. Compared with the findings during her previous entrance, there was a progressive narrowing of the lumen and loss of haustrations of the colon Conclusion: Severe chronic ulcerative colitis

Laboratory Studies—Her blood counts are shown in Figure 4. Differential count showed polymorphonuclear cells 70 per cent, with 50 per cent segmented forms, lymphocytes 17 per cent, large mononuclear cells 6 per cent. Urinalysis, Kolmer and Kline tests were negative. More stool cultures showed no bacteria in the typhoid, paratyphoid A, B or dysentery groups Intradermal tests with coccidiodin and brucellin were negative. Serum proteins: albumin 2 gm per cent, globulin 2 9 gm. per cent.

Treatment and Progress—During the first seven days the former low residue, milk-free diet and sulfasuccidine, crude liver extract intramuscularly, vitamins and antispasmodics were given with no reduction in her symptoms. Then the writer's fruit-free, cereal-free elimination diet was ordered, and with interval feedings over 2000 calories were ingested daily. The number of stools and fever gradually decreased, and in three weeks two to three formed stools were passed Fever was markedly reduced and her appetite, strength and weight steadily increased.

Sigmoidoscopy at this time revealed no bleeding ulcers The mucosa was less granular and edematous, though it still bled easily on swabbing.

During the following thirty days in the hospital there were one to three formed daily stools Her blood count steadily increased, even though only one transfusion was administered during the seventy hospital days Her fever fell to 99° F in the fifth week Her former irritability and "inward nervousness" disappeared, and her appetite and strength were normal on discharge In spite of the elimination

diet from which milk, egg and other foods were entirely excluded, her weight had increased from a low of 84 pounds to 117 pounds.

During the last nearly four years her colitis has been under excellent control, except for a few days six months after I first saw her, when for a few days white bread and butter had been taken. Moreover, on two other occasions she ate milk or wheat for one meal with resultant loose stools and cramping for two to three days afterwards. Otherwise, except for the results of probable pollen allergy discussed below, she has passed one to two formed stools a day and has been free of abdominal and rectal distress and soreness.

Because of two or three loose movements with some distention and cramping for a few days in August, 1946, and again four to six loose movements with traces of blood and fever of 101° for a period of two weeks in July, 1947, probable pollen allergy complicating her definite food sensitivity was assumed. During the last two years, desensitization treatment with a multiple antigen containing the spring, summer and fall pollens of her vicinity have been selfadministered in dilutions varying from 1:5,000 billion every three to four days up to the 1:5 billion dilution at the present time. During this last year and a half there has been no return of her colitis, no fever, and no abdominal distress or pain. About four months ago soreness in her right maxillary antrum with pain in her right forehead developed. Examination revealed a chronic maxillary sinusitis confirmed by x-ray findings. In spite of a radical Luc-Caldwell operation and delayed healing of her operative wound, her ulcerative colitis has been under perfect control, due to her adherence to her strict cereal-free and fruit-free elimination diet, plus rice, and extra vegetables, peaches and pears and her continued pollen treatment. Along with this, vitamin C, 50 mg. daily, and one B complex capsule have been given daily. Her present blood count is hemoglobin 85 per cent, erythrocytes 4,500,000 and leukocytes 11,000.

Comment. This control of the colitis during the last nearly four years has emphasized food allergy as the major cause with pollen allergy as a likely secondary factor. The sudden development of this localized allergy in the colon without previous illness often occurs in this disease. That the colon may be the only shock organ of allergy is evidenced in this patient. Her negative family history of allergy moreover is of interest.

The improved blood count, the change from frequent liquid bloody stools with cramping to the infrequent normal solid stools, the gradual reduction of fever, the excellent gain in weight even though milk, eggs and wheat were eliminated are shown in the chart. Since food allergy alone can produce fever, it is possible that the normal temperature (as in Case 4) would have developed without the use of the sulfathalidine. It is also uncertain how much the good results depended on the crude liver extract given intramuscularly three times a week. Without the control of food allergy this adjunctive therapy probably would have been useless. This excellent control during the nearly four years seems to have depended on her strict adherence to the diet and her perennial pollen therapy. This good control is emphasized by the failure of her recent sinusitis and Luc-Caldwell operation to activate her colitis in any way.

Her colitis remains controlled. No sulfonamides or antibiotics have been given in these nearly four years. There are two formed daily bowel movements with no cramping. Her diet excludes milk, wheat, corn, lettuce, citrus fruit, tomatoes, apricots, melons, bananas, spices and chocolate; and pollen therapy is being given by the patient under the writer's direction.

Case 6.—The following case record is included as illustrative of the second group of patients in Table I, where co-operation was limited but where results from the writer's treatment indicated food and/or pollen allergy as the probable major cause.

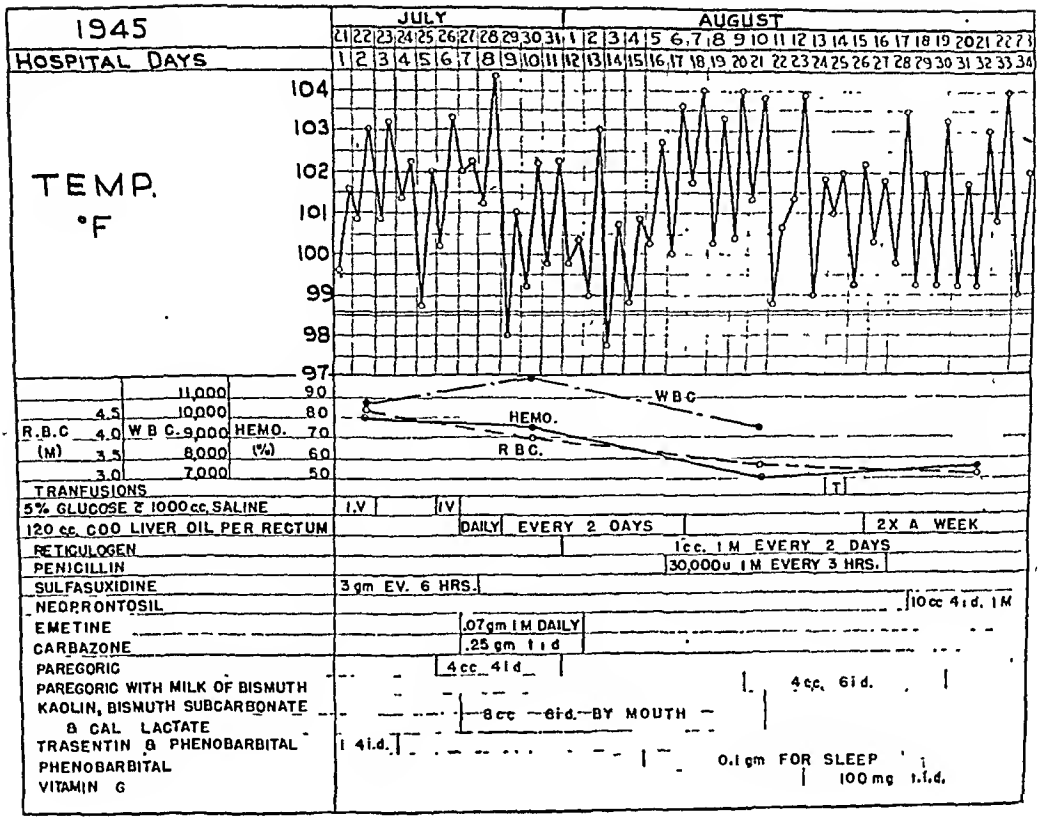

Fig. 5. *Case 6.* Mrs. R. C., aged twenty-six. Chronic ulcerative colitis treated with a high protein, high calorie, low residue diet, and liver extract and various drugs shown in the chart, with no results. Emetine, carbazone, sulfasuxidine and the limited amounts of available penicillin were not beneficial.

Recent follow ups have failed in fifteen of these twenty-one patients. Of the remaining six, symptoms have recurred in varying degrees and frequently in all of them, colonic surgery having been done in four of these patients. In our opinion continued treatment based on allergy as the major cause would have controlled these symptoms in most cases.

A young woman, Mrs. R. C., aged twenty-six years, was first seen at the University of California Hospital in September, 1945, because of chronic ulcerative colitis. For two years before the third month of her pregnancy one and one-half years ago, streaks of blood had been present in normal bowel movements on two or three occasions each week. This blood was absent during the last six months of pregnancy. It reappeared, however, two or three months postpartum for only one month.

On May 30, 1945, blood reappeared in her stools. They became more frequent, and in late June three to four semi-formed stools with some blood and mucus but with no pain were being passed in each twenty-four-hour period. While she was motoring from Chicago to San Francisco in early July, watery stools developed, increasing in number and frequency from every four to every one to two hours. Cramping, urgency and tenesmus with the movements and a persistent fever were present. She entered another hospital in San Francisco on July 21. In spite of the administration of liver extract, penicillin, sulfa drugs, emetin, carbazone and other therapy, as shown in Figure 5, her fever and many watery bowel movements continued. Her laboratory studies gave the following results: Urinalysis was negative. Her blood counts are shown in the chart; her differential count (July 22)

showed polymorphonuclear cells 90 per cent, with 52 per cent segmented forms, lymphocytes 23 per cent. Three stool examinations for ova and parasites were negative. Stool culture for bacteria in the typhoid, paratyphoid and dysentery groups was negative. Agglutination tests for typhoid and paratyphoid were negative.

Roentgen ray studies of the colon showed that haustrations were diminished in the descending colon and absent in the tube-like sigmoid. Small cylindrical areas of increased density in the transverse and descending colon and sigmoid suggested probable ulceration. Impression: early ulcerative colitis.

She was admitted to the University of California Hospital on August 24. There was no previous history of any gastrointestinal symptoms and no history of any clinical allergy or other chronic disease. Her periods had been normal. Her family history also was negative.

Her physical examination showed a weak, thin young woman with a fever of 102° and a pulse of 110. She was passing blood-tinged watery stools with a few blood clots and some mucus. Her abdomen was tender on pressure over the lower portion. No rigidity, organs or masses were felt.

Laboratory studies gave the following results. Urinalysis was negative. Blood counts are shown in Figure 6. Differential count (August 24) showed polymorphonuclear cells 79 per cent, with 67 per cent filamented forms, lymphocytes 24 per cent, large mononuclear cells 1 per cent. (Four differential counts done during her stay in the hospital gave similar results.) Kohlmer test was negative. Four stool examinations for parasites and ova were negative. Two stool cultures for bacilli in the dysentery, typhoid and paratyphoid groups were negative. All agglutination tests for typhoid, paratyphoid, tularemia and brucellosis were negative. Prothrombin time was 65 per cent of normal. Serum proteins: (September 11) albumin 2.3 gm. per cent, globulin 2.15 gm. per cent; (October 23) albumin 3.75 gm. per cent, globulin 2.65 gm. per cent.

Sigmoidoscopy with low spinal anesthesia showed a narrow rectum and sigmoid with multiple small polyps in the mucosa. There was a firm granulomatous ulcerated mass 3 by 4 cm. in size on the anterior rectal wall. The mucosa was erythematous and granular in appearance, and much bloody mucus was present.

Treatment and Progress.—The same type of diet, liver injections and medications given in the first hospital along with B. vitamins by vein and four transfusions were administered during the first eighteen days at the University Hospital. The bloody stools increased in number. The fever persisted and finally she became incontinent, confused and depressed. A rectovaginal fistula developed. On the nineteenth day the writer's fruit-free elimination diet was started, and during the first week incontinence and delirium gradually decreased and the stools decreased in number. Some soft and a few formed stools were passed (Fig. 6). Seven days later thrombophlebitis developed in both legs, and a bilateral ligation of the femoral veins was done. Six days later a massive hemorrhage from the rectum occurred, requiring transfusions on two successive days.

In spite of the above complications her fever continued to decrease, and soft or formed stools up to eight in twenty-four hours with a decreasing content of blood. were passed. Her strength gradually returned and her appetite improved. Abdominal pain and soreness disappeared by October 4, she was ambulatory October 16, and gained six pounds in the last fourteen days in the hospital.

During the first ten days at home she gained another 10 pounds and her stools reduced to five or six a day along with two or three slight additional discharges of mucus. She returned by train to Chicago two or three weeks thereafter. Another physician advised a soft bland diet. At that time, however, she reported a further gain in weight and ability to do some of her housework and shopping, before the soft regular diet was taken.

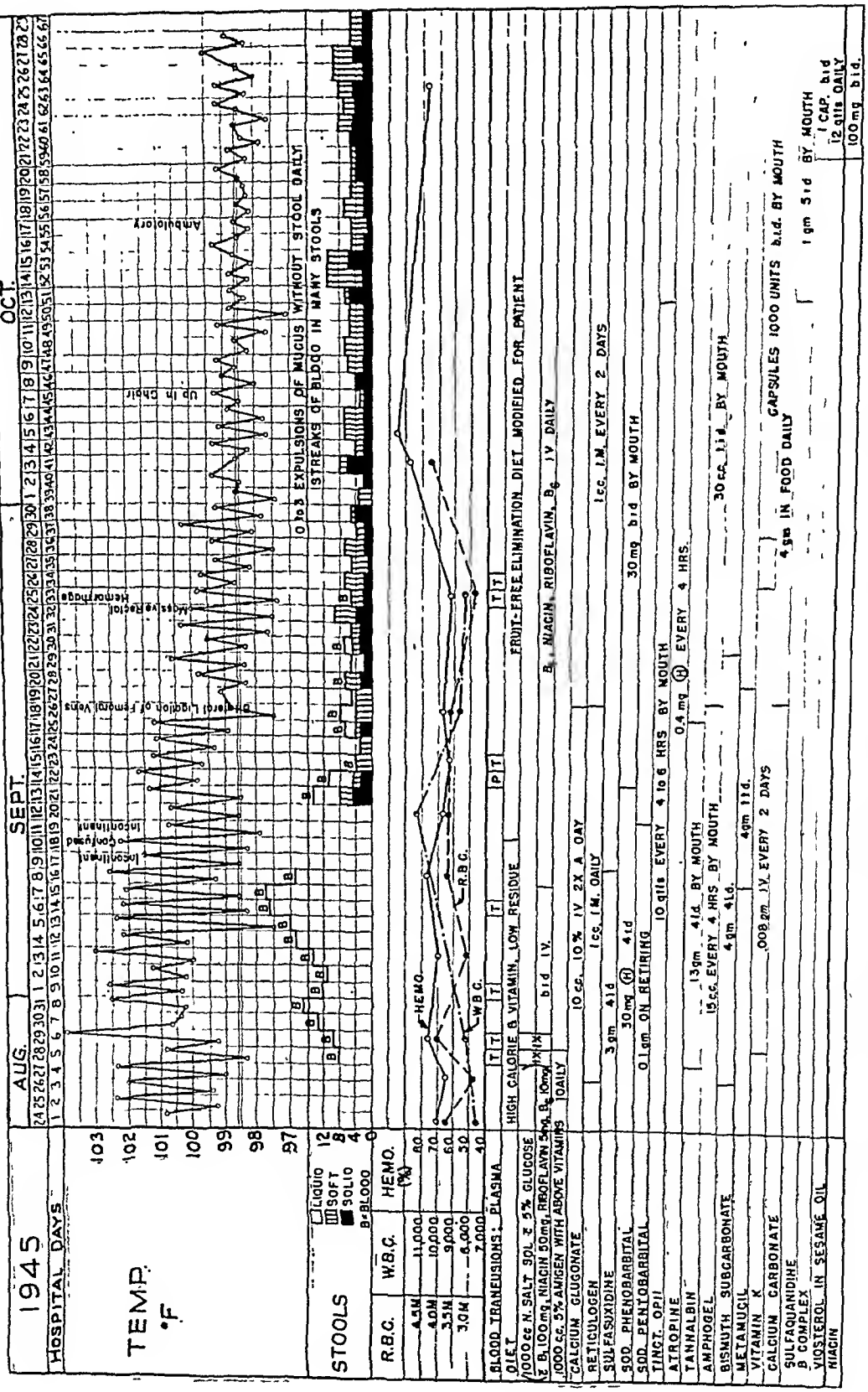

Fig. 6. Case 6. Mrs. R. C., aged twenty-six. With the same treatment and diet which had failed in the previous hospital (see Figure 5) diarrhea and blood increased, incontinence and confusion developed. Then with the modified fruit-free elimination diet, solid and soft stools developed in three days. Sulfasuxidine and all antidiarrheal and antispasmodic drugs were stopped except phenobarbital, tincture of opium, atropine and amphogel. Today these later drugs would have been stopped sooner or not prescribed. The steady improvement was not interrupted by the bilateral ligation of the femorals, and the large massive hemorrhage. The rapid and steady improvement with the elimination diet is in striking contrast to the lack of benefit with the usual nonresidue, high calorie diet and the many drugs ordered in the first hospital (Fig. 5) and during the first eighteen days in the second hospital.

July 11, 1946: A letter reported "wonderful health" until January, 1946. Then colitis recurred, requiring hospital care for six weeks. Streptomycin was given intramuscularly and later by mouth. Retention enemas of bismuth subgalante were administered twice a day, and a high calorie, high protein, high vitamin diet without the exclusion of any specific foods was prescribed. During the next two or three months she gradually recovered, and in the last two or three months her colitis was inactive and her weight was 125 pounds.

October 13, 1947: A letter reported the birth of a nine pound boy in July, 1947. Since her last letter there had been no recurrence of her colitis except for five to six watery stools each day during the fifth to seventh month of her pregnancy. Moreover during pregnancy her rectovaginal fistula discharged again and gradually ceased draining during the last month. She was comparatively well, doing some of her housework and caring for her two children. Her weight was 123 pounds.

January 13, 1948: A letter on this date stated that in December, 1947, her colitis was well controlled and a proctoscopy had revealed no ulcerations and an "almost normal bowel." Only rough foods were excluded from her diet.

On January 25, 1948, her stools increased from two soft movements to four or five in each twenty-four hours. Then her stools rapidly increased up to twenty liquid ones a day. She was placed in the hospital where streptomycin, penicillin, tincture of opium and other drugs were given without help for five weeks. An ileostomy was done and after six weeks she left the hospital having gained 15 pounds up to 126 pounds.

During the rest of 1948 she felt "tops," though the ileostomy was a "nuisance." She had eaten everything except roughage. "I still have two more operations if the colon again discharges blood, mucus and pus." No bleeding or discharge from the rectum had occurred, however, for several months.

Comment.—In our opinion the control of food allergy was responsible for the rapid relief of diarrhea, the gradual reduction of fever and blood in the stools and the gain in weight after this writer's treatment was initiated with a modified fruit-free elimination diet on the nineteenth day in the second hospital in 1945. This relief occurred even though the patient had been incontinent and confused during the preceding days and sulfasuxidine had been stopped. It continued and increased even though a bilateral ligation of the femoral veins was done and a massive hemorrhage occurred. During the next three months while this elimination diet was continued there was a gain of 16 pounds and a return of strength and energy.

Because of this excellent result it is our opinion that continued consideration of food allergy would have been wise. Individual foods should have been added gradually to the elimination diet, excluding any which re-established symptoms. The addition of cereal grains including wheat, egg, chocolate, and spices especially should have been delayed for weeks, and because of the great frequency of milk allergy in chronic ulcerative colitis it should have been eliminated for one or more years. It is generally recognized that milk is not necessary for the maintenance of nutrition and increase of weight, providing ample meat protein and calcium are included in the diet. This is exemplified by the increase of weight in other cases reported in this paper and especially by an increase of weight from 67 to 117 pounds in a young girl of fourteen years whose severe ulcerative colitis has been well controlled during the last year with a milk-free diet and pollen therapy, and by adequate gains in weight in many other patients who have had no milk for months or even years.

When symptoms recurred in this patient, the elimination diet which had yielded spectacular relief in 1945 and saved her from a recommended ileostomy while under this writer's care should have been resumed. With the bland general diet which was given, a recurrence of colitis recurred in two months, invaliding her for three

months thereafter. The relief which occurred for the next year can be explained by prolonged refractoriness to the causative food allergens which so often occurs in clinical allergy as already discussed in this paper. Then during the fifth to seventh month of her pregnancy, bloody, loose movements recurred, indicating a temporary reactivation of probable allergenic causes. Refractoriness continued for another seven or eight months after pregnancy terminated. Then a severe recurrence developed which failed to respond to a soft bland diet with milk and other treatment, because of which her present ileostomy was done. Thus during less than two and one-half years while her former bland, soft diet was eaten, there were two severe exacerbations and one moderate exacerbation of her ulcerative colitis.

It is our opinion that with the continued consideration of food allergy these exacerbations probably would have been prevented. During the exacerbations which did occur, the writer's elimination diet should have been resumed. Thus the ileostomy might have been prevented. This opinion is supported by many prolonged good results similar to those in Cases 2, 3 and 4 in this contribution.

This chronic ulcerative colitis developed in the early twenties with no previous history of gastrointestinal symptoms, no previous allergic manifestations and no familial predisposition to chronic or allergic disease. All of this in no way excludes the possibility of allergy as the underlying major cause of the chronic ulcerative colitis. Allergy in the colon may start as in other body tissues without any familial predisposition to allergy and the colon may be the only shock organ of allergy in the body. As is frequent, traces of blood had been in her stools on and off for three years, except for the last six months of her pregnancy, during which various manifestations of allergy as asthma or eczema may disappear, to reappear one or three months postpartum for varying periods of time.

SUMMARY

1. That an eczematous-like inflammatory reaction to food and less often to pollen and at times to other inhalant and drug allergies is the primary cause of chronic ulcerative colitis is indicated by the writer's study and treatment of this disease in the last twelve years.

2. When allergy is the sole cause, the symptoms gradually reduce or disappear with the control of the allergies.

3. When complicating infection, anemia, hypoproteinemia or avitaminosis are present, their treatment also is necessary.

4. Allergy best explains the primary lesions. Localized vascular allergy can cause the erythema, edema and a friable and easily bleeding mucosa. Granulation, erythema and oozing are also the main features of active atopic dermatitis. The herpetic ulcers can arise from minute vascular thromboses which also cause canker sores, the latter being due to food and at times to drug and bacterial allergies. With low resistance, secondary infection causes fever, fistulae, abscesses, perforation and peritonitis.

5. Remissions can be explained by the tendency to refractoriness to causative allergens or even to anergy which develops in clinical allergy, explaining recurrent asthma, allergic headaches or angioneurotic edema. The seasonal occurrence of symptoms due to pollen allergy and the decreased or absent symptoms in the summer months due to food allergy help to explain variations of symptoms.

6. The tendency for allergy to localize in specific tissues and to limited

areas of one tissue and the spreading tendency of atopic dermatitis can explain the localization and spreading characteristics of chronic ulcerative colitis.

7. Fever may arise from allergy, especially to foods or drugs, though complicating infection is the usual cause.

8. Treatment therefore should take food and pollen and to a lesser extent other inhalant and drug allergies into account in all cases of ulcerative colitis.

9. In mild cases the writer's fruit-free elimination diet and later on his minimal elimination diet usually control food allergies.

10. In fulmination cases the writer's strained meat liquid formula, containing 100 to 150 grams of protein and 2000 calories, together with additional lamb, potato, tapioca and sugar as tolerated, is advisable for the study of food allergy. Intubation of this formula is possible with nausea and severe anorexia.

11. Suspected pollen and inhalant allergies require strict environmental control, pollen and dust filters and desensitization with multiple antigens, as advised by the writer.

12. Complicating infections demand sulfa drugs and the new and older antibiotics, as indicated by the patient's response and tolerance to them. Aureomycin, Chloreomycetin® and Salazopyrin are of special help.

13. Anemia and bleeding require transfusions and iron if tolerated. Vitamin K and Rutin may be necessary.

14. Hypoproteinemia requires the advised high protein elimination diet, transfusions and human albumin.

15. Cramping, diarrhea and pain may require careful use of codeine and at times tincture of opium. Sedation is contraindicated, except at times with small doses of barbitals. Antispasmodics are disappointing and usually inadvisable.

16. Ileostomy with the usual total colectomy is contraindicated until adequate and experienced treatment based on probable food or inhalant allergy and possible drug allergy has been used for an adequate period as advised by the writer. When "early ileostomies" are done before such treatment is given, they are not justified in spite of the low mortality with antibiotics and present surgery.

18. Surgery should be reserved for those cases where perforation and peritonitis threaten life in spite of the vigorous use of the sulfa and antibiotic drugs or where uncontrolled perianal infection or abdominal abscesses or intestinal infection are continuing in spite of present therapy. Then, postoperatively, probable food, pollen or drug allergies must be adequately considered in treatment, particularly if any part of the colon, which is the shock organ of allergy in these patients, remains.

(References on Page 819)

TESTING FOR IDENTITY AND PURITY OF POLLEN EXTRACTS

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USERS of commercial pollen, who take the precaution to examine microscopically the batches as purchased, occasionally find them too badly contaminated for use, and sometimes even wrongly named. Though this condition has received little notice, its prevalence is indicated in the report by Ellis and Dahl (1947), which is possibly the only one in the literature. They state that, "By microscopic examination of 260 different lots of dry pollen purchased from commercial sources . . . 6.5 per cent was incorrectly labeled, and 5.4 per cent was seriously contaminated." The serious contaminations ran from 2 to 87 per cent of foreign pollens, and involved as many as eight different plant families in a single lot. Notice was taken of this condition by Veldee (1948) in recommending to collectors that batches of pollen be not contaminated with foreign pollens to a greater extent than 1 per cent, and that the collector or his immediate supervisor be well grounded in taxonomic botany.

It has been the experience of the writer that when excessive contaminations or misidentifications are brought to the attention of the collectors, they nearly always show themselves to be genuinely appreciative, and willingly replace the defective lots, so that it can be safely said that the defects are rarely, if ever, knowingly incurred, and it is to be hoped that some improvement will result from the application of Dr. Veldee's recommendations. This can best be advanced if consumers of commercial pollens carefully examine all lots of pollen, both microscopically and serologically, and reject those that do not conform to the recommendations.

Ellis and Dahl state that "the identification of a pollen extract is made with considerable difficulty, and the identification of contaminants in an extract, practically impossible." "The identification of pollen grains," they say, "is made with certainty and relative ease by a person properly trained." I find myself not in complete agreement with these statements. It is true that one can detect mislabeled and contaminated pollens by miscroscopic examination, providing the species under consideration have sufficiently distinctive morphological characters, but this is by no means always the case.

On the other hand, if the pollens are antigenically different, they may always be distinguished by their serological reactions. If they are antigenically identical, their distinction is not important.

In order to distinguish two pollen extracts, or to detect contamination of one with the other, it is necessary to procure two allergic sera with sensitizations to each of inverse dominance. It is not necessary that either be

From Lederle Laboratories Division, American Cyanamid Company.
Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

TABLE I

Sites sensitized with		Tests with unknown extracts						Test with dominant allergen 1000 u p ec		
		1000 u p ec		2000 u p ec		2000 u p ec				
		w	e	w	e	w	e		w	e
Rod serum Bermuda dominant	H	9	45	6	25	0		Bermuda	9	50
	J	10	50	7	15	0		Bermuda	0	
	K	10	45	7	30	0		Bermuda	0	
	L	10	50	6	30	0		Bermuda	0	
Jam serum, Timothy dominant	H	9	45	0				Timothy	0	
	J	9	50	0				Timothy	0	
	K	9	45	0				Timothy	6	30
	L	9	45	0				Timothy	0	

Reactions to pollen extracts of Bermuda, timothy and mixtures of the two (designated H, J, K, L) of sites sensitized with a Bermuda dominant and with a timothy dominant serum After desensitization of the sites of each serum by H, J, K and L, they were tested with the allergens of their dominant sensitizations.

The fact that H had failed to neutralize the Bermuda sensitization, but had that of timothy, shows that it contains no Bermuda grass and is therefore pure timothy Similarly K is shown to be pure Bermuda grass Since J and L both neutralize the dominant sensitization of each serum they must both be mixtures of Bermuda grass and timothy W indicates the diameter of the wheal and e that of the erythema; u.p. ec denotes Noon units per c c

the over-all dominant sensitization of its serum; thus, one serum often can serve in several identifications, if it possesses many sensitizations of varying degrees of dominance.

Bermuda grass and timothy were chosen to put this thesis to the test because their pollen grains are almost indistinguishable microscopically, and differentiating sera are readily available (1947). Four extracts were submitted for examination. They were Bermuda grass, timothy, Bermuda contaminated with timothy, and timothy contaminated with Bermuda. They were designated by letters (H, J, K, L) without revealing which was which.

Two sera* were chosen, one in which Bermuda grass was the sole dominant with no reciprocals, and the other in which timothy was dominant but reciprocal with orchard grass, perennial ryegrass, sweet vernal grass and redtop. Four sites were sensitized on one arm of a normal recipient with the Bermuda dominant serum, and four symmetrically opposite on the other arm, with the timothy dominant serum The sensitizations were made by injecting intracutaneously 0.05 c.c. of the sera diluted 1:10. Twenty-four hours later the sites were tested with the unknown extracts, H, J, K and L, injecting 0.01 c c in appropriate dilution in the different sites (Table I). After the sites were completely desensitized to the unknown extracts, each was tested with the pollen of its dominant sensitization Bermuda reacted only with the site that had been neutralized by H, and timothy only with that neutralized by K of their corresponding sensitizations, showing that H contains no Bermuda grass and that K contains no timothy, and since H neutralizes its timothy dominant site to timothy, and K neutralizes its Bermuda dominant site to Bermuda, H is identified as pure timothy, and K as pure Bermuda grass. The other two unknowns neutralize both

*The sensitization patterns of these sera have been reported (1948), designated as Jam and Rod sera

the Bermuda and timothy dominant sites; hence they must be the impure samples containing both pollens.

It is often possible, when the contamination of an extract is slight, to tell which is the preponderant pollen. In this case the first reactions of J and L were both maximal with both sera and without significant differences. Nevertheless, they failed to neutralize their Bermuda dominant sites, so these were retested, and the retests show that J had come much closer to doing it than had L. Hence, it appears that J is the Bermuda contaminated with timothy and L is the timothy contaminated with Bermuda. After these conclusions had been reached, it was revealed that H was pure timothy, K was pure Bermuda, J was Bermuda with 3.5 per cent timothy, and L was timothy with 3.5 per cent Bermuda. The method is, therefore, capable of distinguishing the pollen of one grass from another and revealing contaminations of one with the other by as little as 3.5 per cent. In the case of the Bermuda grass, the identification is absolute because Bermuda grass is the sole dominant of its serum, with no reciprocals. But with the timothy, the identification is not so specific. It could as well be orchard grass, perennial ryegrass, sweet vernal grass or redtop, since these are reciprocal with timothy. However, it is doubtful if these grasses are antigenically distinct.

A similar experiment was done to see if it is possible to distinguish bur ragweed from sagebrush singly and as contaminations. Spri and White sera were chosen. The sensitization patterns of these have been reported elsewhere (Wodehouse, 1948, 1949). The dominant sensitization of Spri serum is to ragweed, with short, western and bur ragweeds reciprocal. Sagebrush is subordinate and reciprocal with marshelder, burweed, cocklebur and slender ragweed. It partly neutralizes the sensitizations to western, short and tall ragweeds but not appreciably that to bur ragweed. Hence, the latter was chosen for the experiment. The dominant sensitization of White serum is to Russian thistle, with sagebrush subdominant, being dominant to all sensitizations except Russian thistle and summer cypress. Bur ragweed sensitization of this serum is a weak subordinate, reacting only when both the serum and antigen are used in high concentration, as in the present experiment.

The experiment was done as before (Table II). Four sites were sensitized with the serum in which ragweed was dominant over sagebrush. diluted 1:10, and four with the serum in which sagebrush was dominant over the ragweed, diluted 1:4. Following neutralization of the sites by the unknowns designated as M, N, O, P, it was found that bur ragweed reacted only after neutralization with O, and sage brush only after neutralization with M. Hence, O is pure sagebrush, and M is pure ragweed; N and P are mixtures. Which is which, in this case, is revealed by the first reactions. P gives the larger reaction with the ragweed serum, and N gives the larger with the sagebrush serum. Hence, P is mostly ragweed and N is mostly sagebrush. After these conclusions had been reached, it was

TABLE II

Sites sensitized with		Tests with unknown extracts				Test with dominant allergen 1000 u p. cc		
		1000 u p. cc		2000 u p. cc				
		w.	e.	w.	e.		w.	e.
Spin serum Ragweed dominant	M	10	55	0		Bur ragweed	0	
	N	7	40	0		Bur ragweed	0	
	O	8	45	0		Bur ragweed	8	10
	P	10	40	0		Bur ragweed	0	
White serum Sagebrush dominant	M	7	10	0		Sagebrush	6	20
	N	8	15	0		Sagebrush	0	
	O	9	15	0		Sagebrush	0	
	P	8	35	0		Sagebrush	0	

Reactions to pollen extracts of bur ragweed, sagebrush and mixtures of the two (designated as M, N, O, P) of sites sensitized with a serum in which ragweed was dominant over sagebrush, and one in which sagebrush was dominant over ragweed. After desensitization of the sites of each serum by M, N, O and P, they were tested with the allergens of their dominating sensitizations.

The fact that O failed to neutralize the ragweed sensitization, but did that of sagebrush shows that it is pure sagebrush. In the same way, M is shown to be pure ragweed. And since N and P both neutralize the dominating sensitization of each serum, they must contain both pollens.

revealed that O represented pure sagebrush, M was pure bur ragweed, P was bur ragweed with 3.5 per cent sagebrush, and N was sagebrush with 3.5 per cent ragweed. Owing to the reciprocal neutralizations of the ragweed serum the ragweed could as well have been short or western. However, it is extremely doubtful if any antigenic difference exists between these species. The sagebrush sensitization, on the other hand, finds no reciprocals in its serum, except to other members of the genus Artemisia, so its identification is definitely to the genus. Further than this we cannot go for it has already been shown that the different species of Artemisia are antigenically identical (Wodehouse, 1948).

These experiments establish the fact that if sites are sensitized with two sera possessing inversely dominant sensitizations, tested and desensitized with an unknown extract, then each tested with the allergen of its predominating sensitization, one positive and one negative reaction indicate that the unknown extract contains only the allergen that failed to give a reaction; both tests negative indicate both allergens present; and both tests positive indicate neither present. This may be expressed graphically as:

$$a \rightarrow X \rightarrow A \begin{cases} \nearrow + = \text{A absent from X} \\ \searrow o = \text{A present in X} \end{cases}$$

$$b \rightarrow X \rightarrow B \begin{cases} \nearrow + = \text{B absent from X} \\ \searrow o = \text{B present in X} \end{cases}$$

if a and b represent reagins, A and B their homologous allergens, and X the unknown solution.

(References on Page 814)

PERSISTENT COUGH AND BRONCHOSPASM DUE TO EXPOSURE TO FUMES FROM RANGE OIL

A New Clinical Syndrome

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ABOUT nine years ago, while staying at a summer camp, I developed a short, hacking cough, which lasted three days and then ceased, only to recur in the same way on the following weekend. Suspecting that it might be the oil range, exposure to which in the past on several occasions had given me a laryngeal "catch," I gave it no further thought until several months later when a patient presented himself with a clinical history similar to mine. With elimination of the oil range, he had a complete permanent remission.

During the following winter, a three-year-old boy was referred to me for studies. He had suffered from a continuous hacking cough, worse in the winter and more marked at night, and associated after the second year with wheezing. He came from northern Maine and had been in Boston for three days when his symptoms ceased. The cough was so similar to mine that a diagnosis of nonpassive expiration asthma due to range oil fumes was made. Subsequent experimental change of environment proved that exposure to range oil fumes almost always caused coughing and wheezing. Absence of exposure to the fumes of range oil was associated with complete freedom from symptoms.

Gradually, with further experience as the clinical picture became more clearly defined, more patients presenting the full constellation and its associated syndromes were recognized, and in all, some forty-one case-histories have been gathered together in the subsequent nine years.

In the average patient, the onset is so insidious that he cannot ascribe an exact date to his initial symptoms. The cough usually comes on in the fall as early as the first cool days, and in New England, while ragweed pollen is still prevalent. The cough grows worse with the onset of winter, reaching its utmost in severity by March or April. In some patients it may decrease or become completely quiescent during the summer months, depending, of course, upon the pattern of life followed in the patient's home.

For the younger children, who are not as yet in school, the symptoms may be continuous. Those at school may have periods of freedom during the week, with exacerbations during the weekend, being much worse when bad weather keeps them indoors and improved when in the outside air. For older people, the ones at home, usually the housewife, is worse off than her husband or sons unless their occupations keep them at home, as it does among coastal fishermen and farmers, who in the sections further north have minimum outdoor winter activities. Not all members of the

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family are equally affected, the very young and the very old being the chief sufferers.

In patients who have suffered a long-standing cough of this type there may be an associated sinusitis, a bronchitis, a history of frequent upper or lower respiratory tract infections, progressing to a chronic bronchitis. Young and old present an emphysema, the former due to the constant forceful expiration, which in the latter is also associated with changes due to age. In the absence of infection there is little or no phlegm, the cough being low in the throat and therefore often completely nonproductive. It is recalcitrant to any and all drug treatment, except for massive doses of narcotics which, of course, are acting, in all the doses given, as general sedatives rather than cough depressants. In these patients expectorants have no expectorant action, and the cough, chronic, persistent, hacking and unproductive, keeps the patient awake and often makes life miserable for the members of his family and occasionally his neighbors who cannot possibly escape it and stay asleep. In some families several members may be affected, their symptoms differing only in degree. The elimination of the oil for the patient most seriously ill has resulted in decreased illness for all of his group. Occasionally, however, only one person shows this spastic response.

When wheezing develops, it is severe and the patient becomes a medical emergency. Removal to the hospital changes the environment, and so these patients, who do not directly respond to the medicines given them, nevertheless improve, going from dire illness to complete recovery in two or three days. To the despair of the patient, his family and the physician, the cough may recur within an hour or two after returning home or may be delayed for one or two days, presenting itself as a short double expiratory hack every few minutes, gradually growing more severe and continuously barking before developing into a wheeze. It may occasionally begin as a catch in the throat, and some patients have learned that they are sometimes relieved by keeping water boiling continuously on the very stove responsible for their symptoms. This may decrease the marked dryness, but does not markedly affect the basic irritation.

When the patient resides in such geographical areas in which oil stoves are in general use, he may experience no clinical change related in any way with change in environment. His symptoms are present at his friends, his relatives, the corner general store, the local garage, the post office, and the club. Sometimes, to add to his mystification, exposure will not result a cough. A mild winter may expose him to more fresh air and lessen his symptoms, while a severe winter may expose him to more of the irritant fumes which make him much worse. At his lowest point, the very nadir of his symptoms, when he is chronically fatigued and worn down by lack of sleep, infection, usually a pneumonia, may intervene, and if the patient is treated away from home, both conditions are successfully cured, the one, of course, to recur. Those patients who have suffered successive pneumonia

for several succeeding winters may go south or southwest and, by the elimination of the range oil fumes, rather than the geographical location, become completely well.

In some there is, naturally enough, a personal or family history of allergy. They follow dust precautions and take injections of house dust with no effect. Some are given vaccines, stock or autogenous, achieving questionable results. Careful study in some of the larger medical centers usually leads to a diagnosis of psychoneurosis. Some of these patients have had psychotherapy, with which no fault can be found since the organic cause being unknown, a functional reason, arrived at by exclusion, was postulated.

One of our male patients was diagnosed as suffering from "a depletion syndrome" and given a high caloric, high vitamin diet and testosterone, responding well while hospitalized but proving himself completely recidivist with a relapse on returning home.

One of the two case histories to be given is illuminating, in that the patient presented a concomitant pansinusitis, supposedly the cause of his wheezing but nevertheless still present and causing no symptoms following elimination of the exposure to range oil fumes.

The patient, fifty-five years of age, presented symptoms which began in August, 1944. Skin tests by four allergists at intervals since have been completely negative. A chest x-ray is said to have demonstrated a mass, for which a bronchoscopy was done. No diagnosis was made, and the mass has since disappeared. X-rays of the sinuses showed both antra to be dense. The patient was given emergency treatment for acute bronchial asthma in August, September, October and November of 1946, each attack clearing completely during a hospital period of three days. Some small polyps were removed in January, 1947. A diagnosis of pansinusitis was made, and the patient was hospitalized again for acute bronchial asthma in February, 1947. While in Florida for all of March he was symptom-free. Two days following his return in April he required hospitalization. The cough persisted daily with severe wheezing for one night in June, three in July and two in August and then with increased frequency, several times monthly with three hospital admissions for emergency treatment in September, followed by continuous wheezing for the winter months. Elimination of range oil on March 3 gave him an almost complete remission to date (June 1), except that one Luasmin capsule was taken on March 8 because he thought an attack (which, by the way, did not materialize) was imminent. He overate on March 23 and suffered from dyspnea lasting approximately thirty minutes, which however required no medicine. He gained 11 pounds in six weeks. He sleeps all night and on the occasion of his last visit reported that for the first time in five years he had been able to spend an afternoon splitting logs.

The second patient's history is classical in its simplicity. A girl of five was seen on April 28, 1948, because of a catch in her throat associated with a short, hacking cough and difficult breathing. Her symptoms were occasionally present during the day but were always worse at night, reaching a climax at about 3:00 a.m. Wheezing attacks occurred at intervals of several days and lasted three days for four attacks in October. There were occasional remissions up to one month. On the same day, and before she returned home from the physician's office, the stove, which was of a gas and oil type, was turned off, with complete remission, lasting now for exactly one year.

The laryngeal bronchospasm, when due to exposure to range oil fumes, is apparently caused by the end-products of the combustion of kerosene (range oil, coal oil) in the wick variety of burner of the type surrounded by three perforated cylinders and known to act on "the reverse flame principle." With this type of burner, the air is sucked by natural draft into the holes of the perforated shells which surround the space which is filled with oil vapor, due to the vaporization of the kerosene which lies at a constant level in a receptacle at the base of the wick, the yellow flames of which merely vaporize the oil. The true flames, which are blue, consist of air burning in an atmosphere of hydrocarbon gas, in accordance with what is known as the aldehydeous combustion process.

Any cause of incomplete combustion, as for instance when the cylindrical shells are too cold, when there is not sufficient air, or when the level of the oil is not exactly right, leads not to the formation of soot, which is a product of destruction, but to the occurrence of invisible acrid vapors containing aldehydes. These aldehydes are the typical intermediate products of this type of blue flame combustion. The asthma seen in warmer parts of the country where coal oil stoves are used only intermittently for occasional cold spells is probably due to these fumes.

The long-chain hydrocarbon molecules in kerosene burn gradually, like fuses, forming first high alcohols, then fatty acids and aldehydes or peroxides, which are themselves gradually transformed into lower alcohols, organic acids and aldehydes, at the same time splitting off formaldehyde molecules. These eventually burn separately either to carbon dioxide and water or to carbon monoxide and water, or are broken down thermally to carbon monoxide and hydrogen.

An imperfect burner of this type gives off acrid, invisible, tear-drawing vapors without the slightest trace of soot. These vapors invariably contain varying amounts of formaldehyde. Some patients are affected by a little, while others require larger doses before symptoms occur.

This process is quite different from that seen in a kerosene lamp, in which the center of the flame consists of pure hydrocarbon vapor exposed to strong radiation of heat from surrounding flame fronts, resulting in a decomposition of the oil gas in the center before it has an opportunity of combining with oxygen. The carbon particles thus formed are set glowing as they reach the flame front on its inner side and are burned as they gradually traverse the flame to its outer side. The kerosene lamp is an example of the carbonic type of illumination as compared to the aldehydeous combustion, and when imperfect, it deposits soot and does not form aldehydes, formaldehyde, or methane.

The fumes are not seen with fuel oil or with a pot-type of burner as used in some heaters using range oil. The venting of the stove may sometimes help, but since the wick is upright and directly beneath the stove venting is never complete. The older the stove the worse the fumes; but the older the house, frequently the better the patient, since the newer

houses have fewer structural defects providing unwanted ventilation. The wick, which may be asbestos or fibre, is apparently not important, excepting as the level of the oil may cause the deposition of soot or gums on part of the wick, resulting in incomplete combustion. The higher the quality of the oil, the less difficulty, but no oil is completely free of the causative materials, since they are due to the type of combustion rather than to the composition of the oil.

The kerosene or range oil as stored does not itself cause difficulty, although in some patients as fumes in clothing they bring on an attack. Some of the patients are also sensitive to other nonspecific irritants, as smoke from coal (soft or hard), wood fires, refrigerant gases, frying oils which are being heated at too high a temperature so that acrolein and other burned products are given off, and in some cases, to tobacco smoke, more from pipes and cigars than from cigarettes.

Since Metazene mist combines with unsaturated sulfur and nitrogen compounds and will completely neutralize formaldehyde, it will be interesting to note its effect on these patients as the present studies are extended.

Of the utmost importance is the fact, however, that these patients, when bronchospastic, are with very few exceptions (and these perhaps more coincidental than real) labeled as intrinsically asthmatic. Infection, however, when present is not causally related to their symptoms. The range oil fumes may, of course, act as a nonspecific irritant in those otherwise atopic.

Since any cough due to any cause may cause marked active expiratory effort and this in itself can lead to bronchospasm, a special descriptive term is warranted.

In actuality, the range oil fumes cause a chronic coughing, leading to bronschospasm. Since, medically speaking, our thinking is usually in reverse sequence, these patients must be labeled as having a wheeze due to continuous nonpassive expiration caused by a chronic cough following exposure to fumes from range oil.

A careful search of the literature has brought to light no previous description of this syndrome, the existence of which must have been suspected and known although not described. If it has been previously described, the reference would be welcomed by the author so that the full credit can be given.

75 Bay State Road

AEROSOLS

I. The Urinary Excretion of Inhaled Phenolsulfonphthalein Mists

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SINCE the initiation of penicillin aerosol for topical therapy of the lungs by the Chemical Corps (then the Chemical Warfare Service) in 1942, the way in which antibiotic aerosols are deposited in the respiratory tract has not been adequately scrutinized.[1,1] This communication is part of a series which will endeavor to place the use of aerosols on a more quantitative basis.[1] The experiments with phenolsulfonphthalein aerosols were begun by one of us (H. A. A.) in the spring of 1946, when the standard solution of phenolsulfonphthalein used in renal function tests was orally inhaled as an aerosol. This solution contained 6 mg. of the dye per c.c. Although traces of the dye appeared in the urine, it was evident that this concentration was too low to lend itself to quantitative experimentation. Further investigations with Reiter in 1947 placed the excretion of the dye after inhalation on a more practical basis for the study of lung absorption (permeability). Finally 2.5 c.c. of a sterile solution of the dye, containing approximately 50 mg. of the dye per c.c., was used in a De Vilbiss No. 40 nebulizer equipped with nasal tips. These tips fit so snugly in the nose that with inspiration, with the air or oxygen at 10 liters per minute, the aerosol acts as if it were in a closed system, goes directly to the lungs through the nose. None escapes into the atmosphere except that exhaled. However, only a part of the dye delivered by the nebulizer actually reaches the lungs themselves. Deposition occurs in the nose and the pharynx with a certain amount swallowed. Nevertheless, this technique apparently provided a simplified approach for the study of aerosols in man because a fairly consistent curve of renal excretion occurred in normal and allergic individuals. In our preliminary work, it was shown that within two hours, 4 to 10 mg. of the dye were excreted in the urine, with the total dye in the urine reaching a limiting value at approximately eight hours. In our first group of five normals approximately 8 to 10 mg. of the dye appeared in the urine within two hours. Later experiments, however, disclosed that this value was rather high and that ostensibly normal individuals could excrete much less. Several questions arose. Since deposition occurs in the nose, what was the effect of shrinkage on the nasal mucous membrane? What effect would the stabilization of the particle size by means of glycerol have on the deposition and absorption of the dye in the lungs?[1] How much of the dye on the nasal mucosa was absorbed into the blood stream

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The authors are indebte[illegible] and Dunning, Baltimore, Maryland, for supplies of phenolsulfonphthlialein.

TABLE I.

URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN—VENT OPEN

Nasal route except in A-3 where oral route was used. Original volume in nebulizer—1 c.c., except in A-8 and A-9 where 1.5 c.c. was used.

Experiment	Original Dye in Nebulizer Mg.	Dye Delivered on Nebulization Mg.	Completion Time Min.	The dye excreted in mg. is given in hours: 1, 2, 3 and 4. The numbers in parenthesis refer to the number of c.c. of urine excreted for each period.			
				Hours:			
				1	2	3	4
A-1 (CR)	39.5	14.5	12	0.85 (632)	0.62 (463)	0.30 (165)	0.26 (93)
A-2 (BK)	39.5	4.9		0.41 (568)	0.12 (323)	0.02 (80)	
A-3 (BK)	66.0	29.0	15	1.44 (375)	1.80 (450)	1.09 (75)	0.74 (50)
A-4 (CR)	66.0	18.5	8	1.52 (198)	1.07 (516)	0.56 (215)	0.34 (75)
A-5 (JS)	66.0	17.5		1.64 (180)	1.59 (155)	0.79 (85)	0.60 (65)
A-6 (CR)	82.0	10.5	5	1.11 (415)	0.72 (440)	0.33 (74)	0.36 (77)
A-7 (BK)	82.0	7.0		1.03 (668)	0.51 (78)	0.13 (66)	
A-8 (CR)	146.0	36.0	10	6.11 (490)	3.58 (230)	2.12 (95)	1.17 (155)
A-9 (HA)	146.0	46.0	10	1.93 (101)	1.45 (110)	1.20 (65)	0.65 (40)

No irritation except in A-3. A-9 had cough, fever and prostration 3 hours after experiment.

and appeared in the urine? What fraction of dye delivered to the patient appeared in the urine? Not all of these questions have been fully answered. However, sufficient data have been accumulated to give in this communication a further report on the urinary excretion of the nebulized phenolsulfonphthalein under various conditions and to make more explicit certain problems connected with (1) aerosol therapy of the lungs in general and (2) the administration of toxic and antigenic aerosols with standardized nebulizers.

METHOD

In general, the method briefly described[2] was employed with certain differences. The standard procedure for renal function was followed except that the dye was inhaled. The bladder was emptied and the subject took 500 c.c. of water. Specimens were obtained hourly from the start of the inhalation. Since, in Tables III and IV, it was assumed that the volume velocity recorded on the flow meter at the beginning of the tube connected to the nebulizer was approximately equal to that at the end of the nebulizer, the value for the volume velocity may be slightly less than given. Nasal tips and L-tube of the De Vilbiss No. 640 combination were employed. The dye was determined by means of a Coleman spectrophotometer. Urinary pigments introduce an error of 0.2 to 0.3 mg. at low concentrations of

TABLE II. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN
Time of each experiment, 15 minutes. Vent was open. Nasal route was used. An initial volume of 2.5 c.c. was used, with 125 mg. of the dye.

Experiment	The dye excreted in mg. is given in hours: 1, 2, 3, and 4. The numbers in parenthesis refer to the number of c.c. of urine excreted for each period.			
	Hours:			
	1	2	3	4
B-1 (CR)	5.0 (200)	2.7 (165)	1.2 (55)	0.63 (45)
B-2 (CF)*	2.9 (315)	1.9 (100)	1.1 (70)	0.88 (70)
B-3 (JS)	6.1 (320)	3.7 (200)	2.3 (145)	1.5 (80)
B-4 (MT)	6.1 (120)	2.1 (90)	1.25 (70)	0.42 (55)
B-5 (CR)**	5.7 (75)	3.3 (45)	1.65 (165)	0.95 (40)
B-6 (BS)*	3.2 (40)	2.3 (40)	1.25 (40)	0.75 (35)

*These subjects are allergic and showed no reaction.
**Had slight irritation. Reaction of fever and cough.

dye. In the A and B series of experiments (Tables I and II) air pressure with a Gast pump was obtained. In the remaining experiments, oxygen was utilized. Some of the subjects preferred the oxygen to the air pump. Whether this preference was psychological or not has not been ascertained.

It is important to note that the dye was nebulized only when the finger was placed over the Y-tube so that the time of nebulization was markedly influenced by the inspiratory pattern of the subject. This will be taken up in detail in a subsequent communication.

It is believed on the basis of experiments now in progress that for every 10 mg. of dye swallowed, not more than 0.5 mg. of the dye will appear in the urine. In general, nasal deposition and swallowing will represent a small constant error in the experiments and under present circumstances cannot readily be avoided. Quantitative data with radioactive solutions might yield better data, but they are technically so difficult that it appears more pertinent to our present therapeutic procedures with antibiotics and sympathomimetic amines to study the behavior of a simple substance like phenolsulfonphthalein where deposition of the dye is readily observed in the nose and pharynx and its excretion can be easily followed in the urine. The presence of dye in coughed-up pus is always observed and studied, as previously reported.[2]

TOXICITY

Reactions (cough, fever and weakness similar to a virus infection) have been observed on five occasions after inhaling the dye. It is not known whether these reactions are due to (1) irritation by the dye, (2) activation of a virus, (3) sensitization to the dye or (4) accidental occurrence of

respiratory infection. In any event, about 100 inhalation tests have been made in which no reaction to the dye was observed. Thus, one of us (B.S.) has inhaled the dye more than ten times with no irritation or reaction whatsoever.

Our animal toxicity experiments may be briefly summarized: Three white mice, approximately 50 gm. each and nine months old, were exposed to phenolsulfonphthalein aerosols, in which the dye was nebulized for seven hours over a period of three days. There were no objective differences from the controls receiving saline aerosols. Three gray mice, each weighing 30 gm., three months old, were given 1 c.c. of the dye intraperitoneally, each c.c. containing 18 mg. Within ten minutes, the nose, tail, ears and the skin became red. The injected dye was readily observed in the blood vessels of the ears. There was no obvious effect on activity as compared to the controls. The skin coloring disappeared within six hours. Red colored urine was observed in the cage. Higher concentrations were then given intraperitoneally with 2 c.c. of the dye containing 18 mg. per c.c. to three gray mice. The same three gray mice were used as in the previous experiments. In 3.5 minutes the body became red and the animals became listless in twenty minutes. This effect wore off in seven hours when the mice became indistinguishable from animals which had no intraperitoneal injection. A fourth experiment was done in which six gray mice received phenolsulfonphthalein aerosol in a dessicator for six continuous hours. The animals were killed and at autopsy nothing abnormal was found. Sections were made of the animals killed immediately, three hours and seventeen hours after exposure. There were no microscopic changes observed. Animals which had received phenolsulfonphthalein intraperitoneally and the saline controls were killed fourteen hours later. In both sets of animals there was evidence of peritonitis. In the animals given the dye, application of alkali to the lungs, kidney and liver showed that the dye still persisted.

EXPERIMENTAL RESULTS

Table I contains experiments designated as Series A. These were undertaken to determine the approximate effect of initial concentration of the dye in the nebulizer on the urinary excretion of dye, in order to ascertain the minimum concentration which would give reproducible and significant concentrations in the urine. In addition, they represent one type of procedure recommended currently for aerosol therapy. Experiments A-1 through A-7 utilized 1 c.c. of the liquid as the initial volume in the nebulizer with a dye content as noted in the table. Inhalation was continued by the subject until the nebulizer failed to operate because of insufficient volume of liquid. These data are of significance because they indicate the possibilities of irregularity in the delivery and absorption when a similar procedure is followed with antibiotic therapy. After experiments A-1 to A-7 were completed, it was believed that the dye excretion in the urine was

TABLE III. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN
Time, 15 minutes. Vent closed. Nasal route used in each case.

Experiment	PSP Solution Nebulized	Diagnosis	Mg Delivered to Patient and Per Cent Delivery	The dye excreted in mg is given in hours The numbers in parenthesis refer to the volume of urine excreted for each period			
				1	2	3	4
C-1 (CF)**	100,000 u penicillin G with 67 mg PSP in 2 5 cc	Bleeding duodenal ulcer and lues	30 mg. 55% del	1 7 (450)	1 8 (150) 2½ hrs	1 0 (90) 3½ hrs	0 5 (60) 4½ hrs
C-2 (WC)	100,000 u penicillin G with 67 mg. PSP in 2 5 cc	Diabetic acidosis	21 mg. 70% del.	1 0 (180)	0 8 (125)		
C-3 (LV)	100,000 u penicillin G with 100 mg PSP in 2 5 cc	Post AP and schistosomiasis	42 mg 58% del.	2 0 (100)	1 4 (45)	1 3 (38)	
C-4 (CF)**	1,000,000 u penicillin G with 66 mgms in 1 2 cc H_2O and 1 cc saline		22% del.	0 8 (145)		1 1 (180) 3½ hrs	
				Serum penicillin levels 0.26 u at 1 hr.—0.1 u at 2¾ hours			

**Same patient.

probably too low. The volume of the dye in the nebulizer was increased to 1.5 c.c., the total dye in the nebulizer being 146 mg. and the experimental time ten minutes. At this time it was noted that with this technique the depth of inhalation might markedly influence the absorption and excretion of the dye, although this could not be ascertained. There are wide differences between experiments A-8 and A-9. In experiment A-8, almost 10 mg. of the dye was excreted in two hours, with only 36 mg. being delivered to the subject. In experiment A-9, less than 4 mg. was excreted even though the subject retained 46 mg. of the dye. The reaction of H. A. A. to the dye in experiment A-9 with cough and fever was subsequently shown by C. R. in a later experiment. The reactions to the dye will be discussed in detail in a future communication. Table II is the second series of experiments performed with the dye in a further attempt to standardize the study of lung absorption and permeability with phenolsulphonphthalein. The preliminary screening experiments in Series A showed that adequate urine excretion was accomplished by inhaling the aerosol produced by a 10 per cent solution for ten minutes. Despite the negative results of the toxicity experiments in animals, it was still believed that the dye might be irritating to the pulmonary mucosa. A reduction of dye concentration to 5 per cent with an increase of the experimental time to fifteen minutes was decided upon to offset the disadvantages of the higher concentration of the dye. In these experiments, the nebulizer vent was open. As in the experiments with injected dye and the nebulized dye in Series A, readily detectable quantities of the dye appeared in the urine ten to fifteen minutes after the start of the inhalation of the aerosol. The data in Table II show that considerable quantities of the dye appear in the urine after two hours. However, there

are wide differences in the quantity of dye appearing in these normal subjects. On the basis of these data, there is a certain element of regularity in the appearance of the dye. Thus subject C. R. showed at the end of two hours 7.7 and 9 mg. of the dye. There is an important difference, however, between C. F. and J. S. which cannot be accounted for by any obvious differences of the two subjects or by the presence of pathology. Because of the occurrence of two reactions, experiments were continued as in Series C, illustrated in Table III, in which penicillin was administered together with the dye. The experiments were conducted, as in Series B, with the exception of C-4. The experiments in Table III illustrate that the presence of penicillin in dye-penicillin mixtures apparently does not interfere with the absorption of the dye in the lung. It is of interest that these experiments were conducted under conditions resulting in 22 per cent to 70 per cent nebulization of dye (the nebulizer residue was rediluted) even though the total experimental time was always fifteen minutes. Evidently we are dealing with variables which are not necessarily in the equipment but inherent in the method of doing the test. It became of importance to ascertain how reproducible the test was and how other factors influence the results. The electric charge and size of penicillin and the dye are somewhat similar. It should therefore be noted that the delivery of the dye also may indicate the delivery of penicillin and other drugs under the experimental conditions. In other words, subject D. F. probably would have retained 55 per cent of 100,000 units following our procedure. In experiments on the same subject, C-1, and later C-4 where the nebulizer was washed out, because of difficulties in respiration only 22 per cent delivery was obtained. However, fairly high values of penicillin units were obtained in the blood. This shows the advantage of using high concentrations of penicillin in the nebulizer as advocated previously.[1,2]

In Table IV are data which explain certain of the variables mentioned in the introduction. In Column 1 are the initials of the patients and the date; Column 2 is the diagnosis; Column 3 shows the presence or absence of 20 per cent glycerin; Column 4 indicates the presence or absence of Privine to shrink the mucous membrane of the nose. Column 5 is the time in minutes of the experiment; Column 6 gives the volume velocity in liters per minute, and Column 7, the volume of urine. Column 8 lists the mg. of dye in the urine; Column 9 shows the residue in the nebulizer; Column 10, the per cent of dye delivered to the patient; Column 11, the dye in the urine after two hours. In view of the large number of variables present in experiments of this type, it was of interest that in patient A. W. there was good agreement in the volume of dye excreted after two hours. In the first experiment 1.38 mg. of dye was excreted, and in the second an identical amount. This agreement, of course, is accidental. The per cent delivery of the dye is of interest since of 100 mg. of the dye in each experiment, 12.5 mg. of dye was delivered to the patient. Of this 12.5 mg., 10 per cent appeared in the urine in two hours. Since the concentration in

TABLE IV. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN

The vent was closed. When Privine was used, a 0.1 per cent solution was employed. Two similarly calibrated De Vilbiss No. 40 nebulizers were used. Two c.c. of 5 per cent PSP was used as the initial volume and concentration.

Experiment and Date	Diagnosis	Glycerine 20%	Privine	Time in Min.	Volume Velocity 1/m.	Volume of Urine Excreted c.c.		Mg. PSP Excreted		Residue in Nebulizer Mg.	Per Cent Del.	Total in Two Hours Mg.
						Hour		Hour				
						1st	2nd	1st	2nd			
A. W.	Asthma											
(a) 4/7		No	Yes	15	7	30	30	0.63	0.75	—	—	1.38
(b) 4/27		Yes	No	15	7	0	50	0.00	1.38	87.5	12.5	1.38
E. W.	Hay fever											
(a) 4/8		No	Yes	15	8	360	325	0.63	0.85	—	—	1.48
(b) 4/15		No	No	15	7	140	320	0.50	0.27	85.0	15.0	0.77
(c) 4/22		Yes	No	15	7	280	230	0.56	0.68	92.5	7.5	1.24
(d) 4/28		Yes	No	15	7	390	160	0.75	0.65	95.0	5.0	1.40
T. A.	Gangrene of right toe	2.5%	PSP									
(a) 4/13		No (b	y Mo.)	10	5	410	300	0.00	0.002	41.6	19.0	0.002
(b) 4/19		Yes	No	15	7	475	105	0.75	0.22	89.0	11.0	0.97
(c) 4/21		Yes	No	15	7	450	240	1.05	0.67	89.6	10.4	1.72
J. I.	Bronchiectises											
(a) 4/14		No	Yes	15	7	310	160	3.38	3.00	86.1	13.9	6.38
(b) 4/21		Yes	Yes	15	7	240	90	2.34	2.45	90.0	10.0	4.79
(c) 4/28		Yes	Yes	15	7	230	80	2.05	2.04	83 0	17.0	4.09
M. K.	Hay fever											
(a) 4/15		No	Yes	12	7	530	320	1.75	2.3	78.0	22.0	4.05
(b) 4/22		Yes	No	15	7	570	330	1.15	1.6	89.8	11.0	2.75
(c) 4/29		Yes	Yes	15	8	410	220	1.50	1.23	85.0	15.0	2.73
D. F.	Infectious mononucleosis											
(a) 4/27		Yes	No	10	7	—	190	—	0.58	—	—	0.58
(b) 5/3		No	No	15	8	70	35	0.33	0.24	87.5	12.5	0.57
F. P.	Prepyloric lesion											
(a) 5/25		No	No	15	7½	200	75	1.4	2.1	72.0	28.0	3.5
(b) 5/27		No	No	15	9	200	210	2.15	3.0	75.0	25.0	5.15
(c) 6/3		No	No	15	8½	315	120	1.95	2.15	77.5	22.5	4.10
(d) 6/9		No	No	15	8½	235	210	1.71	2.43	75.5	24.5	4.14

the urine after an intravenous administration of 6 mg. of the dye would be about 70 per cent of the dye administered, it would appear that approximately between 10 per cent and 20 per cent of the dye delivered to the patient in this way, appeared in the urine in two hours. In patient E. W., four experiments, (a) (b) (c) and (d), were done in which these variables were studied in more detail. It was found, however, that there was considerable variation in the amount of dye delivered to the patient. In addition, of some interest is the fact that in E. W.'s experiment (b) less than 0.8 mg. of the dye was delivered in two hours even though more of the dye was delivered to the patient by nebulization. This experiment emphasizes the fact that there were still variables which had to be considered. In patient T. A., 2.5 per cent solution of the dye was delivered by mouth because the 5 per cent solution was irritating. This experiment is excellent from the point of view of studying the effect of swallowing the dye. Prac-

tically no dye was excreted. At the end of two hours there were in experiment T. A. (b) 0.97 mg. of dye in the urine and in (c) 1.72 mg. of dye. After four hours, the same discrepancy appeared even though the delivery by the nebulizer was fairly constant. Patient J. I. had extensive bronchiectasis which did not respond to various types of penicillin therapy. He took the dye well except for the fourth time, when a reaction occurred. In two hours his excretion varied from 4 to 6.8 mg. Although this patient was experienced in breathing aerosols, it was nevertheless surprising to find the high excretion of the dye in the presence of extensive lung pathology. Similar experiments with patients M. K. and D. F. again showed the fluctuations. The data in Column 9, where a fairly wide difference in delivery of the dye under constant experimental conditions may be observed, offer a clue to the possible cause of the variation. The delivery of dye varies from 5 per cent to 20 per cent even though the total time of the experiment and the volume velocity of delivery of the gas is fairly constant. The experiments on patient J. I., and on the experienced normals in Tables I and II, as well as on patients with deep inspirations, were observed to be followed with higher excretions of dye. This led to the point of view that the variations were not so much due to baffling by the nose or the stability of the aerosol but to the conditions of experiment, in all likelihood connected with the character of inspiration or the inspiration time.

It is well known that the longer an aerosol is retained in the lung the greater the probability that the particles will be deposited; in other words. the greater the probability of collision of particles with the mucous membranes of the respiratory tract, the greater the probability of deposition. For this reason, it was decided to continue these studies in which not the total time of administration of dye was of importance but the *inspiration time*. An inspiration-time meter was devised which is described in a following paper of this series. This device measures the actual time in which the aerosol is inspired, the number of inspirations, and by means of auxiliary devices gives the character of the respiratory cycle as well as the total time. Since the volume velocity of the gas, the amount of dye delivered, and the conditions of delivery are known, a balance sheet may be obtained, in which more explicit data of the conditions under which the deposition of the dye in the respiratory tract occurs may be visualized.

DISCUSSION

These experiments have been reported in full because the present tendency in the use of the therapeutic aerosols is to give the patient the antibiotic or epinephrine, or whatever drug is indicated, in a nebulizer with brief directions and to hope for the best. This casualness in therapy should be replaced by a more quantitative procedure. It has been pointed out in previous communications that it is important to have the delivery of the nebulizers determined. It would be desirable to have the manufacturers of nebulizers certify that a given nebulizer is capable of delivering a given

quantity under specified conditions. Although it is not practical at this time to certify nebulizers in the way that thermometers are certified, in view of the fact that antibiotic, especially penicillin, aerosol therapy of the respiratory tract has become a standard procedure in the treatment of lung infections,[1] it appears that the errors inherent in the accidental variations of aerosol therapy are more than anticipated. Certainly, the data presented in Tables I to IV show that under ostensibly controlled conditions, with standardized nebulizers, with a substance as easily determined as phenolsulfonphthalein, there is probably great variation in the deposition in the lungs. Only by a study of the data, as indicated in the body of the paper, may the reader visualize how important the standardization of aerosol therapy is for the successful completion of topical therapy by means of aerosols.

SUMMARY

By means of phenolsulfonphthalein aerosols data have been obtained on the absorption of phenolsulfonphthalein from the lungs following inhalation of aerosols of this dye. The experiments were mainly carried out using the nasal route so that inhalation occurred in a closed system. The effect of baffling by the nose and upper respiratory tract as well as swallowing of the dye is shown to be of minor importance with the main quantity of the dye appearing in the urine dependent upon absorption through the mucous membrane of the lungs.

The study of the toxicity of phenolsulfonphthalein aerosols in mice showed that large quantities of this dye can be safely injected and inhaled without serious toxic effects. Five reactions in man have been observed during a course of about 100 tests of aerosol inhalation with fairly concentrated solutions and quantities of the dye. These reactions have been fever, cough and general weakness similar to a virus infection endemic in the vicinity where the experiments were done. Whether these reactions are due to irritation by the dye, activation of a virus, sensitization to the dye or accidental occurance of respiratory infection has not been ascertained. Otherwise there was no irritation produced by the dye administered in the way described.

The following variables have been studied and data presented pertinent thereto: (1) Effect of the initial concentration of the dye in the nebulizer on urinary excretion of the dye, (2) The effect of increasing the volume of the dye, (3) The effect of shrinkage of the nasal mucosa, (4) Absorption from the nasal mucosa and excretion in the urine, (5) the effect of glycerine to increase deposition and absorption of the dye in the lungs, (6) The reproducibility of renal excretion of the dye, (7) The ratio of the dye excreted in the urine to the dye delivered by the nebulizer to the patient. It is concluded from the experiments that a larger number of

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COMPARATIVE TOXICITY AND SIDE EFFECTS OF THE ANTIHISTAMINIC DRUGS

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THE ANTIHISTAMINIC drugs now in general use relieve symptoms in many forms of allergy—especially hay fever, vasomotor rhinitis and urticaria—but they also produce undesirable results, or side effects. Because of wide differences in the frequency and in the severity of the toxic reactions reported in human subjects, it is important to record the comparative toxicity and side effects of the various antihistaminic drugs.

The following drugs were compared at essentially equal therapeutic dose levels: Benadryl, Pyribenzamine, Neo-Antergan, Antistine, Histadyl and Neohetramine. These drugs were chosen because they are the most widely used. All contain the dimethylaminoethyl radical, with differences in the remainder of the molecule. The chemical structures are shown in Figure 1.

CLINICAL STUDY

Side effects were recorded only in patients receiving therapeutically effective doses. Many of the patients reported in this study have been taking several different antihistaminic drugs interchangeably from one to four years without disturbance in blood count, blood chemistry or urine. The present study is a comparison of the toxic effects produced with the use of Benadryl in 217 cases, Pyribenzamine in 126 cases, Neo-Antergan in 127 cases, Antistine in 97 cases, Histadyl in 89 cases, and Neohetramine in 111 cases.

TABLE I. RESULTS OF TREATMENT WITH BENADRYL

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	11	7	4	63.6
Vasomotor rhinitis	44	19	25	43.2
Bronchial asthma	80	24	56	30.0
Chronic urticaria	21	11	10	52.4
Acute urticaria	32	26	6	81.3
Miscellaneous allergies	29	12	17	41.4
Totals	217	99	118	45.6

Benadryl.—Two hundred and seventeen patients received Benadryl for symptomatic relief in seasonal and nonseasonal hay fever, acute and chronic urticaria, atopic and contact eczema, bronchial asthma, and miscellaneous allergies, as pruritus, allergic pharyngitis, gastrointestinal allergy, allergic conjunctivitis, migraine, vernal catarrh, and drug allergy. Doses of 50 mg. were administered whenever necessary for intermittent symptoms, and 50 mg. four times daily for continuous symptoms. Dosage had to be adjusted in many patients according to individual requirements. The dosage schedule employed was considered adequate because it was thera-

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peutically effective. Results of treatment with Benadryl are recorded in Table I, and the side effects in Table II.

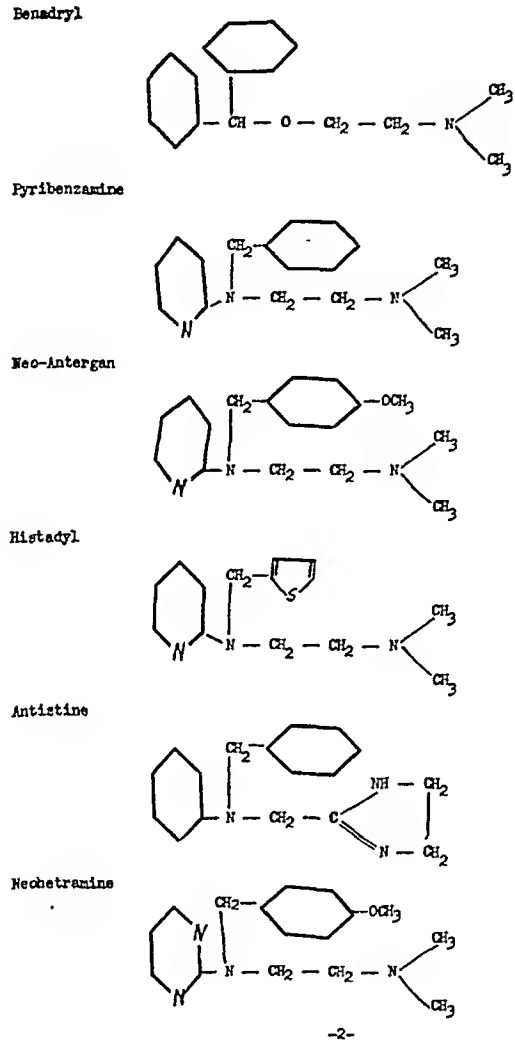

Fig. 1.

Of 217 patients treated with Benadryl, 133 (61.3 per cent) complained of side reactions. In fourteen cases side effects were so severe that the drug had to be discontinued. Drowsiness, the most common, occurred in ninety-three (42.9 per cent) but gradually diminished in most patients and in some cases entirely disappeared with continuance of the drug. Dryness of the mouth occurred in forty-four patients; tingling, weakness or heavy sensation of the hands in thirty-two; headache in twenty-one; dizziness in fifteen; nervousness in eight; vomiting in four; weakness in two, and diarrhea in one. Patients complained of one to four different side effects, but most reported that the untoward reactions either diminished or disappeared as treatment continued. In several cases there were unusual

reactions: mental in-co-ordination in three; narcolepsy in two; and one patient slept for twenty-four hours after one 50 mg. dose of Benadryl. One felt as though he were "walking on air." Another, after 50 mg. of

TABLE II. BENADRYL—SIDE REACTIONS
Total Cases—217; Reactions—133 (61.3%)

Side Reaction	*Occurrence*
Drowsiness	93
Dryness of mouth	44
Tingling, heaviness or weakness of hands	32
Headache	21
Dizziness	15
Nervousness	8
Tinnitus	8
Vomiting	4
Mental in-co-ordination	3
Narcolepsy	2
Weakness	2
Diarrhea	1

Benadryl, was almost struck by an automobile twice in an hour, and became so emotionally disturbed that she refused to leave the hospital for twenty-four hours. In one case the patient became so drowsy driving his car that he had to park on the side of the road and sleep for two hours.

Pyribenzamine.—This group consisted of 163 cases, as follows: hay fever, 112 cases; vasomotor rhinitis, eighteen cases; bronchial asthma, nine cases; chronic urticaria, six cases; acute urticaria, one case; allergic eczema, twelve cases; and contact dermatitis, five cases. The dosage used was 50 mg. whenever necessary for intermittent symptoms, and 50 mg. every four hours for continuous symptoms. Results of treatment with Pyribenzamine are recorded in Table III.

TABLE III. RESULTS OF TREATMENT WITH PYRIBENZAMINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	112	82	30	73.2
Vasomotor rhinitis	18	10	8	55.6
Bronchial asthma	9	1	8	11.1
Chronic urticaria	6	5	1	83.3
Acute urticaria	1	1	0	100.0
Allergic eczema	12	5	7	41.7
Contact dermatitis	5	3	2	60.0
Totals	163	107	56	65.6

Side effects were recorded for 126 of the 163 patients treated with Pyribenzamine. Of these 126 patients, forty-five (35.7 per cent) complained of side effects, as tabulated in Table IV.

Side effects were fewer and not as marked as with Benadryl, but again unusual reactions were observed in several patients. One, an hour after taking 50 mg. of Pyribenzamine, became comatose for six hours; another was markedly drowsy and showed mental in-co-ordination while driving an automobile. He swerved from one side of the road to the other, several times narrowly avoiding accident. Another patient developed a tachycardia of 140 which lasted about twelve hours.

The usual side effects either diminished or disappeared, although Pyribenzamine was continued on the same dosage schedule. In a group of twenty-one patients taking 50 mg. of Pyribenzamine one to three times

TABLE IV. PYRIBENZAMINE—SIDE REACTIONS

Total Cases—126; Reactions—45 (35.7%)

Side Reaction	*Occurrence*
Drowsiness	17
Dizziness	8
Headache	8
Nausea	4
Nervousness	4
Weakness	3
Dryness of mouth	3
Fatigue	2
Tinnitus	2
Comatose	1
Mental in-co-ordination	1
Vomiting	1
Tachycardia	1
Irritability	1

each day for two years, monthly blood counts, blood chemistry and urine examinations remained normal.

Neo-Antergan.—This group consisted of 141 allergic patients who received 50 mg. of Neo-Antergan two to four times a day, depending on the duration of symptoms. The results of treatment are shown in Table V.

TABLE V. RESULTS OF TREATMENT WITH NEO-ANTERGAN

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	96	67	29	69.8
Vasomotor rhinitis	22	13	9	59.1
Bronchial asthma	15	2	13	13.3
Acute urticaria	1	1	0	100.0
Chronic urticaria	2	1	1	50.0
Allergic eczema	1	0	1	0.0
Pruritus	1	1	0	100.0
Angioneurotic edema	1	1	0	100.0
Vernal catarrh	1	0	1	0.0
Contact dermatitis	1	1	0	100.0
Totals	141	87	54	61.7

Of 141 patients receiving Neo-Antergan, thirty-five (24.8 per cent) experienced side effects (Table VI), most of which were mild and disappeared as the treatment was continued without change of the dosage schedule. Diarrhea (in eleven cases) was more frequent than with Benadryl, Pyribenzamine or Antistine. In this group there were no unusual or severe side effects.

TABLE VI. NEO-ANTERGAN—SIDE REACTIONS

Total Cases—141; Reactions—35 (24.8%)

Side Reaction	*Occurrence*
Drowsiness	13
Nausea	11
Diarrhea	11
Abdominal cramps	8
Headache	4
Dizziness	3
Tachycardia	4
Weakness	2
Sweating	2
Pruritus	2
Fatigue	1
Dryness of mouth	1
Vomiting	1
Nervousness	1

Antistine.—Antistine was administered to 111 patients. Ninety-seven of this group received 100 mg. (the therapeutically effective dose) every four hours whenever necessary to control symptoms, and side reactions were carefully recorded. Twenty-two (22.7 per cent) reported side effects. Table VII summarizes the results of treatment with Antistine and Table VIII the side reactions.

TABLE VII. RESULTS OF TREATMENT WITH ANTISTINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	80	45	35	56.2
Vasomotor rhinitis	17	9	8	52.9
Bronchial asthma	6	0	6	0.0
Chronic urticaria	5	4	1	80.0
Acute urticaria	1	1	0	100.0
Allergic eczema	2	1	1	50.0
Totals	111	60	51	54.1

TABLE VIII. ANTISTINE—SIDE REATIONS

Total Cases—97; Reactions—22 (22.7%)

Side Reaction	*Occurrence*
Drowsiness	6
Nausea	6
Headache	3
Dizziness	2
Tachycardia	2
Gastritis	2
Diarrhea	1
Fatigue	1
Nervousness	1
Sores in mouth	1
Insomnia	1
Abdominal cramps	1
Pruritus	1
Pharyngitis	1
Vomiting	1
Constriction of chest	1

In this series the usual side effects were encountered, as with Benadryl and Pyribenzamine, but were fewer and less severe. One patient complained of an unusual side effect—constriction of the chest lasting two hours. Because of the possibility of coronary artery disease, she was referred to the hospital. However, her blood pressure remained normal, sedimentation rate was 12 mm. per hour, and the electrocardiographic tracing showed no evidence of coronary disease or myocardial damage. Two weeks later, administration of 100 mg. Antistine by mouth again produced constriction of the chest.

Histadyl.—Histadyl was administered to eighty-nine allergic patients in doses of 50 mg. one to three times daily. In patients not relieved, but with no severe toxic reactions, the dose was increased to 100 mg. Therapeutic results and side effects are shown in Tables IX and X.

TABLE IX. RESULTS OF TREATMENT WITH HISTADYL

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	47	36	11	76.6
Vasomotor rhinitis	17	9	8	53.9
Bronchial asthma	13	2	11	15.4
Acute urticaria	5	4	1	80.0
Chronic urticaria	3	2	1	66.6
Allergic eczema	2	1	1	50.0
Contact dermatitis	2	1	1	50.0
Totals	89	55	34	61.8

Of eighty-nine cases, eighteen (20 per cent) developed side effects but no unusual reactions were encountered in this group. Drowsiness and gastrointestinal symptoms were the most common side effects, but drowsiness was not severe enough to warrant discontinuance of the drug.

TABLE X. HISTADYL—SIDE REACTIONS

Total Cases—89; Reactions—18 (20%)

Side Reaction	*Occurrence*
Drowsiness	9
Dizziness	2
Dryness of mouth	2
Nausea	3
Abdominal cramps	2
Weakness	1
Tachycardia	1
Fatigue	1
Nervousness	2

Neohetramine.—One hundred eleven patients received Neohetramine, generally in doses of 50 mg. one to four times a day. In some cases 100 mg. three to four times daily was necessary to relieve the symptoms. In this group also the amount and frequency of the dose had to be adjusted, for many of the patients, to suit individual requirements. The results of treatment with Neohetramine are recorded in Table XI.

TABLE XI. RESULTS OF TREATMENT WITH NEOHETRAMINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever (ragweed)	41	29	12	70.7
Hay fever (timothy)	7	5	2	71.4
Hay fever (trees)	5	4	1	80.0
Bronchial asthma	24	10	14	41.7
Vasomotor rhinitis	22	14	8	63.5
Allergic eczema	6	1	5	16.7
Chronic urticaria	5	3	2	60.0
Pruritus	1	1	0	100.0
Totals	111	67	44	60.4

Of the 111 patients treated with Neohetramine, eight (7.2 per cent) noticed side effects, but no unusual or severe reactions (Table XII). Two patients discontinued use of the drug, one on account of nausea and the other because of an exacerbation of asthmatic symptoms. Seven of eight patients experienced one side reaction, and one patient, two. Mild drowsiness occurred in two and disappeared on further use of the drug.

TABLE XII. NEOHETRAMINE—SIDE REACTIONS

Total Cases—111; Reactions 8 (7.2%)

Side Reaction	*Occurrence*
Drowsiness	2
Dryness of mouth	1
Bitter taste	1
Nausea	1
Fatigue	1
Headache	1
Restlessness	1
Marked nervousness	1
Aggravation of asthmatic attack	1

DISCUSSION

Antihistaminic drugs have an important place in the symptomatic treatment of allergic diseases. Valuable adjuncts to the management of aller-

gies, they are not, however, a substitute for careful determination of specific etiologic factors, elimination of offending allergens where possible, or hyposensitization when necessary. Untoward reactions, not encountered in animal studies,[3,6,8,9] have occurred in human beings, and reports of serious and unusual side effects are beginning to appear in the clinical literature.[1,2,4,5,7,10-16] B. A. Sachs[11] has classified the toxic reactions encountered with Benadryl as neuropsychiatric, alimentary, cardiovascular, respiratory, genito-urinary, muscular and ocular, and it seems that the same classification can be applied to many of the other antihistaminic drugs. Severe untoward reactions are more common with higher doses.

The present study deals only with the side effects observed at therapeutically effective doses. Indeed, the dose schedule was adjusted to give essentially equal therapeutic results with all drugs studied. In general, the side effects, regardless of severity, disappeared within one to twenty-four hours after discontinuing the drugs.

Side effects occurred most frequently with Benadryl, with drowsiness of most common occurrence—in 93 of 217 cases (42.9 per cent). Dryness of the mouth was observed in forty-four of the 217 cases (20.3 per cent). Tingling, heavy sensation or weakness of the hands was reported by thirty-two (14.8 per cent); headache in twenty-one (9.7 per cent); dizziness in fifteen (6.9 per cent); nervousness in eight (3.7 per cent); tinnitus in eight (3.7 per cent). Other less frequent reactions were vomiting and diarrhea. Common side reactions varied from one to as many as four in some patients and were most frequent in the group receiving Benadryl. Benadryl also produced several unusual and severe side effects.

With Pyribenzamine drowsiness occurred in seventeen of 126 cases (13.5 per cent) and was not as marked as with Benadryl. Dizziness occurred in eight (6.3 per cent); headache in eight (6.3 per cent); nausea in four (3.2 per cent); nervousness in four (3.2 per cent); weakness in three (2.4 per cent); and dryness of mouth in three (2.4 per cent). Only occasionally did patients complain of fatigue, tinnitus, vomiting, palpitation or irritability. The common side effects also varied from one to as many as four in some patients.

With Neo-Antergan drowsiness occurred in thirteen cases (9.2 per cent); nausea in eleven (7.8 per cent); diarrhea in eleven (7.8 per cent); and abdominal cramps in eight (5.7 per cent). Those are the most common side effects. Other reactions are noted in Table VI.

With Antistine drowsiness was encountered in six cases (6.2 per cent); nausea in six (6.2 per cent); and many of the common side effects such as headache, dizziness and many others occurred occasionally. As a rule, the side effects encountered with Antistine were less severe than those following Benadryl or Pyribenzamine.

With Histadyl drowsiness occurred in nine cases (10.1 per cent); nausea in three (3.4 per cent); dizziness in two (2.2 per cent); dryness of mouth in two (2.2 per cent); and abdominal cramps in two (2.2 per cent). Other reactions are listed in Table X.

In patients receiving Neohetramine side effects were much fewer and much less severe than in the groups receiving other antihistaminics. With Neohetramine drowsiness occurred in only two cases (1.8 per cent); dryness of the mouth in one (0.9 per cent); nausea in one (0.9 per cent); and the rarer side effects were as shown in Table XII.

SUMMARY

1. The comparative toxicities and the incidence of side effects of Benadryl, Pyribenzamine, Neo-Antergan, Antistine, Histadyl and Neohetramine were studied at dosages adjusted to give equal therapeutic results in 781 allergic patients.

2. Side effects occurred with all six drugs. Drowsiness, the commonest side effect, was most frequent and pronounced with Benadryl. In contrast it occurred rarely and was least pronounced with Neohetramine. The overall incidences of side effects were as follows:

Benadryl, 61.3 per cent in 217 cases
Pyribenzamine, 35.7 per cent in 126 cases
Neo-Antergan, 24.8 per cent in 141 cases
Antistine, 22.7 per cent in 97 cases
Histadyl, 20 per cent in 89 cases
Neohetramine, 7.2 per cent in 111 cases

3. In this study of the comparative toxicity and side effects of the antihistaminic drugs, Neohetramine was found to be the least toxic in therapeutically effective doses.

REFERENCES

1. Borman, M. C.: Danger with Benadryl of self medication and large dosage. J.A.M.A., 133:394, 1947.
2. Geiger, S.; Rosenfield, S. Z., and Hartman, D. L.: Unusual reaction following Benadryl administration. J.A.M.A., 133:392, 1947.
3. Hallenbeck, G. A.: Studies on the effect of thymoxyethylamine (929 F) and N-diethylaminoethyl-N-ethylaniline on gastric secretion in the dog. Am. J. Physiol., 139:329, 1943.
4. Kern, E. C.: Marked toxic side effects of Pyribenzamine. J. M. Soc., New Jersey, 44:374, 1947.
5. Leibowitz, H.; Kurtz, I. M., and Schwartz, E.: Symptomatic treatment of hay fever with Pyribenzamine. New York State J. Med., 47:989, 1947.
6. Loew, E., and Kaiser, M. E.: Alleviation of anaphylactic shock in guinea pigs with synthetic benzylhydryl alkamine ethers. Proc. Soc. Exper. Biol. & Med., 58:235, 1945.
7. Lott, G. N.; Krug, E. S., and Glenn, H. R.: A case report of drug delirium clinically interpreted as being due to Pyribenzamine. Journal Lancet. 48:242, 1948.
8. Mayer, R. L.: Antihistaminic substances with special reference to Pyribenzamine. J. Allergy, 17:153, 1946.
9. Mayer, E. L.; Huttner, C. P., and Scholz, C. R.: Antihistaminic and anaphylactic activity of some a-pyridinoethylenediamines. Science, 102:93, 1945.
10. Rives, H. R.; Ward, B. B., and Hicks, M. L.: J.A.M.A., 140:1022, 1949.
11. Sachs, B. A.: The toxicity of Benadryl. Ann. Int. Med., 29:135, 1948.
12. Schwartz, E., and Levin, L.: Benadryl in the symptomatic treatment of allergy. New York State J. Med., 46:1233, 1948.
13. Schwartzberg, S., and Willerson, D.: Prolonged reaction to Benadryl. J.A.M.A., 133:393, 1947.
14. Slater, B. J., and Frances, N.: Benadryl, a contributing cause of an accident. J.A.M.A., 132:212, 1946.
15. Sternberg, L.: Unusual reaction of hysteria from Benadryl. J. Allergy, 18:417, 1947.
16. Weil, H. R.: Unusual side effect from Benadryl. J.A.M.A., 130:990, 1946.

AN EVALUATION OF NEO-ANTERGAN IN DERMATOLOGY

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LOEW[7] defines an antihistaminic drug as one which is capable of diminishing or preventing several of the pharmacological effects of histamine and which does so by a mechanism other than a pharmacodynamic action diametrically opposed to that produced by histamine. Most investigators are agreed that these histamine antagonists (1) prevent histamine from increasing the permeability of capillary endothelium, thus diminishing its vasodilating action, (2) block action of the drug in the cell, (3) possibly prevent the release of histamine but have little effect on the gastrointestinal tract, blood pressure or heart in therapeutic doses.

The histamine theory, although it does not explain the sole mechanism involved in the "allergic diseases," is inferred from (1) certain similarities between anaphylaxis in animals and allergic reactions in man, and (2) the systemic effects of histamine injected artificially. Not all the symptoms in these dermatoses can be accounted for by the action of histamine, which thus explains the failure of the various antihistaminic drugs in many cases. According to Loew, failure to detect histamine blood levels does not negate the histamine theory because histamine leaves the blood stream rapidly, and extraction methods do not always detect physiologically active amounts.

Antihistaminic drugs are being clinically investigated at present because immunization by histamine or histamine conjugates (hapamine) and the inactivation of histamine by enzymes (histaminase) have been generally failures from the clinical standpoint.

The synthesis of Neo-Antergan* (pyranisamine maleate) was first reported in 1944 by Bovet and Walthert[2] in France under the label 2786 R.P. The physiological effects were described by Dews and Graham[3] in 1946 in England, and by Last and Loew[6] in this country.

Our experience has been similar to that of Arbesman[1] in regard to the comparative studies with the various antihistaminic drugs available at the present writing. Benadryl appears to be the most potent, but the frequency of side reactions, especially sedation, reduces its value in ambulatory patients. Pyribenzamine was generally valuable in cases where allergic symptoms were severe. But there are numerous cases where there is a definite place for a "less potent" antihistaminic, and Neo-Antergan seems to fill that void when other drugs have failed. As regards toxicity, there is no agreement at present among clinicians as to which drug is the least toxic but most effective agent.

Failures of antihistaminic drugs may be due to errors in diagnosis, underdosage, absence of liberated histamine in the tissues, or presence of

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*Neo-Antergan was furnished through the courtesy of Merck & Co., Inc.

other causes for the increased vascular permeability. As Lowell[8] states, there are so-called allergic diseases in which no antibodies can be demonstrated in the circulating blood or by skin testing, but which are wholly or in part caused by psychosomatic mechanisms, endocrine imbalance or nonspecific agents. The delayed effects of the antihistaminic drugs are not known at this time. The possibility of interference with the natural formation of autoantibodies in the blood and tissues remains to be seen. So far, there is no evidence that Neo-Antergan affects the antigen-antibody reaction.

DOSAGE

The dosage schedule was adjusted to the individual case. The initial dose varied from 25 to 50 mg. three times a day. Some patients with atopic eczema were given as high as 400 mg. daily, in divided doses, for four weeks. In acute urticaria most patients received 50 mg. every four hours. Children were given one-half the adult dose, although some tolerated doses of 150 mg. fairly well. In patients with intermittent symptoms, the maximum tolerated dose was taken as required. The impression was gained that patients with true allergic dermatoses could tolerate larger doses than the nonallergic group. Where itching occurred chiefly at night, the usual dosage was 100 mg. at bedtime. The longest period in which a patient was under treatment was ninety days. In those cases where there was no benefit after three weeks, or when persistent toxic side reactions appeared, the drug was discontinued and other medication prescribed.

CLINICAL STUDIES

Neo-Antergan was used in this study on 211 patients with various so-called "allergic" and nonallergic dermatoses, in order to evaluate the drug. The treatment period varied from three to ninety days. Feinberg's[4] criteria for the evaluation of antihistaminic drugs was used throughout this study, including placebo medication, discontinuance of medication to observe recurrence of symptoms, and objective improvement paralleling subjective improvement.

Clinical evaluation of an antihistaminic drug is difficult because the clinical picture may be affected by various known and unknown factors, including (1) change of physicians, (2) personality of physician, (3) psychosomatic influences, (4) seasonal influence, (5) effect of concomitant local and general therapy, (6) possibility of spontaneous cure or desensitization or remission and (7) faulty conclusions on part of patient. It is not possible to avoid these conditions in all cases, but by following Feinberg's criteria, the value of a study of this nature is increased.

In no case was there evidence of sensitization to the drug itself.

Acute Urticaria.—In sixteen cases, the results were as follows: cured seven, temporary improvement while taking the drug in seven and no

results in two. In one case of unknown etiology, a fifty mg. tablet was given every hour for eight hours without any effect on the wheals or angioneurotic edema.

Chronic Urticaria.—Hunter's[5] results with the drug in chronic urticaria were as follows: 10 per cent recurrences, 75 per cent cured and 6 per cent failures. In our series of five cases, apparent cures were obtained in four cases, with failure in one.

Papular Urticaria (prurigo simplex).—In six cases in children in which Neo-Antergan was used, relief from the pruritus was obtained in four, but there was no change in the eruption. This condition has never been proven to be an allergic dermatosis.

Penicillin Sensitivity.—In seven cases of penicillin sensitivity, we did not see any immediate results from the drug except moderate relief from the pruritus.

Exfoliative Dermatitis (secondary type).—Two cases of exfoliative dermatitis developed in patients past sixty following treatment for seborrheic dermatitis. In neither of the cases was the pruritus diminished or the eruption improved by treatment with the drug.

Pruritus Ani.—In this group were eleven cases, all of the primary psychosomatic type. In none of the cases was Neo-Antergan effective in controlling the itching. The patients had to resort to local anesthetic ointments (e.g., intracaine) to control the pruritus.

Atopic Eczema.—Control of the pruritus in this condition is "half the cure" since injury to the skin by scratching often generalizes the disorder. Although this clinical entity is called "allergic eczema," there is no proof at present that histamine is etiologic in some or any of the cases. There were twenty-five cases in this series, ten in children. The best results were in children, five with marked improvement, and moderate improvement in four. In five cases in which there was a generalized eruption, Neo-Antergan therapy was used for three months and the condition cleared, except for a residual eczema of the antecubital areas. The eczema was controlled in these cases by taking the drug when necessary to relieve the pruritus. There was no appreciable improvement in adults with this condition since there was a definite psychosomatic influence in most cases. Pruritus was not diminished until the drug was taken for at least one month. In all cases, the maximum dosage was given at night when pruritus is usually more marked. Results were negligible in two cases of asthma-eczema complex.

Disseminated Neurodermatitis.—We use this term for acute or subacute pruritic erythemas of the face, eyelids and neck and occasionally the

TABLE I. CLINICAL EFFECTS OF NEO-ANTERGAN

Diagnosis	No. of Cases	Complete Relief %	Moderate Relief %	Slight Relief %	No Relief %
Acute Urticaria	16	24	26	15	35
Chronic Urticaria	5	16	35	48	11
Atopic Eczema	25	0	65	25	10
Diss. Neurodermatitis	38	17	40	21	22
Contact Dermatitis	37	16	39	26	19
Pruritus Ani	11	0	21	65	14
Senile Eczema	16	0	25	43	32
Neurogenic Pompholyx	22	12	47	23	18
Dermatophytosis with "id" lesions	31	0	56	34	10

antecubital spaces. These are all psychomatic in origin and only affect adults, especially women thirty to fifty. In thirty-eight cases in which the drug was prescribed for three-week periods, there was no appreciable change in the pruritus or clinical picture. In twenty-two cases in this group, none were improved by Neo-Antergan; sixteen reported slight relief from the intolerate itching. Mild sedation, simple psychotherapy, intravenous calcium and local soothing lotions were most effective.

Contact Dermatitis (subacute and chronic).—We used the drug in a group of thirty-two cases, not only for its antipruritic action, but to observe its ability, if any, to prevent autosensitization. In six cases, the drug did not prevent generalized spread of the eruption. It is possible that the drug was not used in large enough doses in these cases for the full antihistaminic effect to be evident. The pruritus of poison ivy dermatitis was satisfactorily controlled in nine cases, although local therapy was also used.

Nummular Eczema.—In four cases in which the drug was used, there was no change in the lesions or pruritus. This was expected since the cause of this dermatosis is undetermined.

Post-Scabetic Dermatitis.—In twelve cases in which contact dermatitis and reinfection were ruled out, good results were obtained for all.

Dermatitis Herpetiformis.—In two cases where the drug was used for three weeks, there was no effect on the eruption or pruritus until sulfapyridine was substituted. It is apparent that antihistaminics are not indicated in this disease.

Erythema Multiforme.—In four cases of the recurrent idiopathic type, no subjective or objective improvement occurred after three weeks. In one case, an attack was not aborted although the patient had been taking the drug for four weeks.

SIDE REACTIONS

Toxic reactions were mild, transient in most cases and unpredictable. The percentage of side reactions (19 per cent with Neo-Antergan) was extremely low even when a total of 400 mg. was given daily. Moderately toxic symptoms occurred in ten patients, mild side reactions in thirty-two.

The most frequent complaint was nausea. In thirteen per cent of the cases, the patients could not tolerate Pyribenzamine either and complained of insomnia, a "jumpy feeling" in the legs, numbness and vomiting, with both drugs. Symptoms complained of, in order of frequency, were as follows:

	Number Cases
Nausea	14
Dizziness	6
Paresthesias	5
Nervousness	3
Insomnia	3
Weakness	3
Headache	2
Cramps (gastrointestinal)	2
Heartburn	2

CONCLUSIONS

1. Neo-Antergan is useful in certain types of "allergic" dermatoses.
2. Its toxicity is relatively low. Its depressant action is much less than Benadryl.
3. A marked difference in response to the drug is apparent in different cases of the same disease.
4. There was no accumulative action, no evidence of habit formation and no effect on the blood pressure, heart or hemogram in thirty cases investigated.
5. Elimination of the causative agent, desensitization where possible, attention to psychosomatic factors and proper local therapy are considered more important than antihistaminic drugs in their present state of development.
6. Failures were believed to be caused by inadequate dosage, improper timing of dosage or absence of liberated histamine in the tissues.
7. Diagnostic tests with antihistaminic drugs are not reliable since many conditions which are definitely nonallergic may clear up as a result of other factors.
8. The indiscriminate use of antihistaminic drugs as a substitute for a careful history, physical examination and prolonged period of observation is to be condemned.
9. If the physician will learn not to expect too much from an antihistaminic drug, Neo-Antergan should be useful in the "allergic dermatoses" as supplementary therapy.

REFERENCES

1. Arbesman, C. E.: Comparative study of several antihistaminic drugs. J. Allergy, 19:178, (May) 1948.
2. Bovet, D., and Walthert, F.: Ann. pharmaceut. France, Suppl. No. 4, 1944.
3. Dews, P. B., and Graham, J. D. P.: The antihistaminic substance, 2786 R. P. Brit. J. Pharm., 1:278, 1946.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING CHRONIC BRONCHIAL ASTHMA

Report of Two Cases

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SUBCUTANEOUS emphysema complicating bronchial asthma is comparatively rare. In 1945, Schwartz[5] reviewed twenty-six cases reported in the literature. In all of the reported cases the patients recovered on conservative treatment, with the exception of one, in whom multiple neck incisions were performed to permit the air to escape. They were all characterized by cyanosis, dyspnea, subcutaneous swelling of the neck and adjacent parts of the body. Two cases herein reported are similar and the patients made uneventful recoveries. In the second case, however, there was a very extensive involvement of the face, neck, thorax (anterior and posterior), the abdomen, the upper part of the back and the right inguinal region (patient complained of pain a few hours before it appeared).

Extreme pulmonary distention is common during attacks of asthma. There may be a marked narrowing of the lumina of the smaller bronchi. The obstruction is caused by a spasm of the bronchial muscles and in part by a swelling of the mucous membrane with an accumulation of exudate in the lumen of the bronchi. During inspiration the pressure in the thoracic cavity lessens, thus widening the alveoli and bronchioles and permitting air to enter the narrowed passages. With expiration, however, the pressure in the thoracic cavity rises; this tends to lessen the diameter of the bronchioles, and since they are already constricted, collapse ensues. The rupture takes place in the apices and along the mediastinal margins where there is no bony support. Air migrates through the tissues into the mediastinum and neck and may extend to the thorax.

*Case 1.**—I. M., a girl, aged fifteen years, was admitted to St. Joseph's Hospital on November 15, 1947, with the chief complaint of swelling of the neck.

Past History: At the age of five months, the patient was admitted to St. Joseph's Hospital with lobar pneumonia. She made an uneventful recovery. Three months later (eight months of age), she commenced her asthma attacks. At the age of three she was readmitted to the hospital (December 12, 1935) with a diagnosis of asthma. She was discharged on January 5, 1936. During her residency in the hospital, the laboratory examinations revealed the urine to be negative. Blood findings revealed: leukocytes, 8,200; small lymphocytes, 22 per cent; large lymphocytes, 38 per cent; large mononuclear cells, 4 per cent; polymorphonuclear leukocytes, 35 per cent, and eosinophils, 1 per cent. Treatment consisted of an elimination diet and supportive symptomatic measures. The next admission was on November 17, 1937, when, following a cold, she developed asthma. Laboratory examinations showed: hemoglobin, 70 per cent; erythrocytes, 4,260,000; leukocytes, 13,000; small lymphocytes, 8 per cent; large lymphocytes, 17 per cent; large mononuclear cells, 1 per cent; polymorphonuclear leukocytes, 74 per cent; urine—albumin, 1-plus; sugar,

*From the medical service of James E. Phelps, M.D., attending physician in medicine at St. Joseph's Hospital, Paterson, New Jersey.

3-plus, and few pus cells. Repeated urinalysis showed completely negative results. The vaginal smear was negative for pathogenic organisms. She was discharged as improved on November 21, 1937. She came under our observation during the attack of subcutaneous emphysema on November 16, 1947. After her release from the hospital, skin tests were performed and positive reactions noted to many inhalants, ragweed pollens and a few foods. She was placed on an elimination diet, and injection —therapy to ragweed pollens and mixed inhalants was begun. She recovered from the asthma and has attended school regularly since then.

Present History: An attack of asthma began on November 14, 1947, and the next morning at 3:00 a.m. she was suddenly awakened by pain on the right side of the neck; a few hours later, it extended to both sides of the neck and the laryngeal region. She also had coughing, accompanied by pain in the area of the right suprasternal notch. Examination revealed a swelling of the neck, more on the right side, with crepitation in both supraclavicular areas. A few wheezes were present throughout the anterior and posterior regions of the chest. An x-ray examination on November 17, 1947, was negative in both the pulmonic field and the central heart shadow. Laboratory examinations revealed the Kahn reactions to be negative; urine, negative; hemoglobin, 14.5 gm. or 85 per cent; erythrocytes, 4,350,000; leukocytes, 9,700; small lymphocytes, 16 per cent; monocytes, 7 per cent; large mononuclear cells, 2 per cent; neutrophils, 73 per cent, and non-segmented cells, 2 per cent.

Case 2.—The second case was that of an extensive subcutaneous emphysema in a twenty-two-year-old man.

Past History: Asthma began at the age of eight years following an attack of scarlet fever, and it became worse at the age of thirteen, especially in the summertime. In March, 1941, he was found sensitive to pollens, inhalants and some foods.

Present History: Severe asthma followed an upper respiratory infection which began on December 18, 1948. He had not responded to the usual methods of treatment.

Diagnosis and Therapy: Bronchial asthma, vasomotor rhinitis and pollen asthma. He was placed on an anti-asthmatic diet, with environmental restrictions, and was instructed as to the use of allergen-proof material over the bedding. Injections with pollens, dust and the special inhalants were given regularly. He was observed uninterruptedly until 1944 when he discontinued treatment. He continued to remain free of asthma, although occasionally (four to six times a year) he had some wheezing which was relieved by 0.3 to 0.5 c.c. of suprarenalin in gelatin subcutaneously.

Although aminophylline, grains 7¾, was given intravenously, the cough persisted; he was dyspneic, and marked wheezing was evident over the anterior and posterior aspects of his chest. Three hours later, 2 grams of sodium iodide were administered intravenously, and 1 c.c. of suprarenalin in gelatin was injected subcutaneously since he had been previously helped by this procedure. Relief was obtained but it was of short duration. Three hours later, 50 c.c. of 50 per cent glucose were given intravenously and 0.5 c.c. of suprarenalin in gelation was injected subcutaneously. Three hours later, aminophylline, 7¾ grains, was added intravenously and 0.5 c.c. suprarenalin in gelatin subcutaneously. He expectorated a very thick and tenacious, occasionally blood-streaked, sputum throughout most of the night. The next day, the asthma was somewhat relieved; there was less dyspnea with some expectoration. After 50 c.c. of 50 per cent glucose, intravenously, and 0.5 c.c. of suprarenalin in gelatin, subcutaneously, were given, he had a fair day, but coughed almost continuously. The following day he complained of tightness of his throat, and swelling of the neck and face. There was crepitation on digital pressure over the neck, lower

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ANXIETY AS A FACTOR IN ASTHMA

A Case Report

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IN THE PAST few years, allergists have become more conscious of the part played by the psyche in the production and aggravation of the symptoms of asthma. Psychotherapy has produced spectacular results in many stubborn cases of bronchial asthma which have resisted all types of immunization procedures. The following case report shows how well anxiety may affect the course of asthma. The treatment of this patient combined a drastic surgical procedure with a psychosomatic approach.

CASE REPORT

R.E., a nineteen-year-old white man, was first seen with a history of three years of repeated asthmatic attacks. In January, 1945, after two months in the Navy, he was discharged because of a right-sided hernia and bronchial asthma. The bronchial asthma became worse following his discharge, and he was placed in a Naval hospital in California for twenty-three days. During his stay there, a Navy surgeon told him that he had only two years to live. From that time on, he was constantly in fear of his life. He was hospitalized three times before we saw him on April 21, 1947.

His past history was negative except for a right herniorrhaphy done in 1947 and an appendectomy in 1932. His family history showed asthma in a paternal great-grandfather.

Physical examination was essentially negative except for a pale, boggy, nasal mucous membrane, and a few râles throughout the lung fields.

Laboratory and x-ray procedures were negative. Skin tests showed marked intradermal reactions to house dust, feathers, and Alternaria.

Treatment was instituted with immunization and precautions to house dust and Alternaria. This regime brought fairly good results. The patient, for the first time, seemed to think that he was being helped. His confidence increased greatly as the months went by. His first hospitalization under our care was brought about when he found out that I was to be away for three days. When I returned from my trip, I was greeted with a peculiar picture of a steam-engine puffing type of respiration, which was not relieved by epinephrine (1:1000). Heavy sedation finally brought him back to normal.

Five months later he developed influenza associated with an increase of the bronchial asthma. The infection finally cleared with antibiotic treatment, but his asthma gradually became worse. He was hospitalized for the second time. On his second day of hospitalization, his condition became critical. Every known anti-asthmatic procedure was attempted, including intravenous 5 per cent ethyl alcohol, intravenous glucose and aminophylline, helium, oxygen, ether-in-oil by rectum, and sedation. Within an hour three bronchoscopists refused to bronchoscope my patient because of his severe asthmatic state. Large doses of intramuscular sodium phenobarbital gave him momentary rest, but he soon became cyanotic and his pulse became too fast to be counted. Death seemed only a few minutes away. An otolaryngologist was called, and he immediately performed a tracheotomy at my insistence. The patient quieted down after mucus was aspirated from his trachea. His course in the hospital was uneventful from that day.

My surgical colleague and I agreed that this patient should have psychotherapy since it became evident from conversation with the patient that he had a serious anxiety neurosis, manifesting itself by a marked fear of death.

The patient refused psychoanalysis, but in discussing his condition with him in three visits of a half hour each, I found that the Navy surgeon had produced this fear of death with the words "you only have two years to live." When I reminded him that we always have tracheotomy available for him to breathe, if necessary, he seemed to lose most of his fear. Then after I mentioned that he had outlived the two-year prediction, I knew that his fear would vanish. His asthma has never recurred since this last attack in November, 1947.

DISCUSSION

In commenting about this case, I wish to state that extreme circumstances of this sort would not have occurred in a normally adjusted person. Such a person would not have been satisfied with this two-year ultimatum and would have sought more expert advice. This young man was not normally adjusted, as I found out from questioning his parents and friends. As a boy, he had no playmates, read books continually, and was a steady companion of his grandmother. In adolescence, he was rather chubby and would not participate in games or sports. He shunned the opposite sex. When his asthma began, he became more conscious of being different from other boys, and this added to his maladjustment. In order to prove his masculinity, he joined the Navy in December, 1945, but his discharge, two months later, left him with a severe depression. The final blow, which produced the anxiety neurosis, was struck by the Navy surgeon. Today, he has not only lost his asthma, but he is adjusting himself well to his environment. How long this will last no one knows, since these maladjusted individuals tend to revert to their former state under an adverse turn of circumstances.

SUMMARY

1. A case report has been presented in which anxiety was a major factor in the causation of asthma.

2. Tracheotomy was used as a life-saving measure in this case, in which the condition was chiefly precipitated by anxiety.

3. It is suggested that psychosomatic concepts be considered in all cases of asthma, so that these patients may be treated more effectively.

314 Home Savings and Loan Building

SCHOLARSHIP AWARDS

The American College of Allergists wishes to acknowledge its thanks to the following firms for making it possible to give eight scholarships at the postgraduate instructional course in allergy given under the auspices of Baylor University College of Medicine, Houston, Texas, October 31 through November 5, 1949. The firms are: Allergen-Proof Encasings, Inc., The DeVilbiss Company, Hoffmann-La Roche, Inc., Hollister-Stier Laboratories, Luzier's Inc., Marcelle Cosmetics, Inc., Nepera Chemical Co., Inc., Rexair Division, Martin-Parry Corporation, and Schering Corporation.

POLLEN ALLERGY IN THE CITY OF SAO PAULO, BRAZIL

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São Paulo is the second city of Brazil, the third largest of all South America, with a population of 1,400,000 inhabitants. A large part of the population are Italian, Portuguese, Arabian, Japanese, Spanish, and German, or descendants of these people. Therefore, those who previously lived elsewhere had the opportunity of acquiring sensitivity to pollens in their respective countries.

The first contribution to the study of pollen allergy in the city of São Paulo was presented by the author.[2] This consisted of a study and classification of the plants which are capable of causing pollen allergy, including their time of pollination. This was followed by a preliminary report[3] which showed the incidence of air-borne pollen, correlated with the meteorologic conditions and the number of postive skin reactions to pollens in Brazilian people. These results were confirmed by Oliveira Lima et al,[1] with the exception that they did not note the pollen of the eucalyptus. Later the author studied the causes of the rarity of pollen allergy in Brazil.

As a result of these observations the following conclusions in allergy in Brazil, particularly in the city of São Paulo, were reached:

1. Pollen allergy is rarely observed in Brazil, particularly in the city of São Paulo.
2. The Brazilian people are not constitutionally refractory to pollen allergy.
3. Brazilian people are able to acquire pollen allergy when they locate in countries where pollenosis is found.
4. The family history of allergic patients born in Brazil with foreign ancestors may show cases of pollen allergy in parents, grandparents or uncles and aunts.
5. The rarity of pollen allergy depends mainly on the environmental factors.
6. Patients suffering with pollenosis from other countries were relieved of symptoms while living in Brazil.
7. The same race that usually develops pollen allergy in the United States does not develop the disease in Brazil (Japanese, et cetera).
8. The following plants, the pollen of which is capable of causing pollenosis in other countries, were noted in Brazil: *Cynodon dactylon, Pao annua, Chenopodium ambrosioides, Polygonum acre, Rumex crispus* and the genus *Ambrosia (Ambrosia polystachya).*
9. Those who suffered hay fever in other countries gave positive skin reactions to extracts of the same pollens noted in Brazil (see below).
10. Hay fever patients, sensitized to European grass pollen, showed positive skin reactions with extracts from Brazilian grass *(Cynodon dactylon* and *Melinis minutiflora).* The same is observed with allergic pa-

tients sensitized to North American ragweed *(A. artemisiaefolia* and *A. clatior)*. They react in the same way to native Brazilian ragweed *(Ambrosia polystachya)*.

11. The air-borne pollens of major clinical significance in Brazil are: *Chenopodium ambrosioides, Amaranthus spinosus, Cynodon dactylon,* and *Poa annua*. The genus Ambrosia is represented in Brazil by the species *A. polystachya*.

12. The air-borne pollens with minor hay-fever-producing substance are: *Xanthium sponsum, Rumex crispus, Morus alba, Morus migra* and the genus Platanus. Eucalyptus is also included; it is insect borne.

13. The air-borne pollens of unknown or questionable cause of hay fever, occurring in great quantity are: *Melinis minutiflora* (forage grass), and *Parthenium hysterophorus*. The latter was found only in the city of *São Paulo*.

14. Plants of the genera Ambrosia, Amaranthus, and Chenopodium and the grasses *Cynodon dactylon* and *Poa annua* are not found in great quantity.

15. The maximum pollen count in the city of São Paulo per 2 sq. cm. was as follows: *Parthenium hysterophorus,* 42; *Melinis minutiflora,* 40; *Cynodon dactylon,* 15; and *Amaranthus sp.,* 15.

16. The low incidence of pollen allergy in Brazil is obviously the result of the scarcity of hay-fever-producing pollens.

17. Pollen of *Eucalyptus sp.* is only found in large quantities (maximum 100 per 2 sq. cm.) near great plantations and does not have a potent exciting substance causing allergy.

18. There are only three plants *(Eucalyptus sp., Parthenium hysterophorus* and *Melinis minutiflora)* whose pollen concentration is capable of producing hay fever in the city of São Paulo.

19. The pollen of *Parthenium hysterophorus* and *Melinis minutiflora* are probably without potent hay fever substance. The concentration of the latter is fairly constant at certain times in May and June.

20. The pollen of *Melinis multiflora* was in sufficient concentration to produce hay fever in a patient previously sensitive to the grass pollen of a foreign country.

21. The time of pollination of most Brazilian plants of allergic significance is during the rainy season, September to March. The incidence during this period is not great.

REFERENCES

1. Mendes, Ernesto: Introducão ao estudo da flora alergisante do Brasil. Rev. paulista de med., 20:257-316, (May) 1942.
2. Mendes, Ernesto: O problema da alergia polínica no Brasil, particularmente na cidade de São Paulo. São Paulo med., 1:407-418, (July) 1942.
3. Mendes, Ernesto: Estudo das polinoses, particularmente em São Paulo. Rev. paulista de med., (sumário), 31:105-107, (July) 1947.
4. Oliveira Lima, A.; Dias da Costa, P. D.; Pereira dos Santos, P.; and Galeno, R.: Contagem de polens aéreos na cidade de São Paulo. O hospital, 28:103-117, (July) 1945.

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UNUSUALLY GOOD RESULTS IN POLLINOSIS WITH COMBINED ANTIGEN-ANTIHISTAMINE THERAPY, SHORTENING THE TREATMENT OF HAY FEVER

Study I

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THE INTRODUCTION of antihistaminic drugs has given a new impetus to the treatment of allergic diseases. In the past, these drugs primarily have been employed for symptomatic relief, and numerous reports have appeared in the literature attesting their palliative effectiveness.

The possibility that antihistaminic preparations can assume a major role in hyposensitization therapy has received scant attention. Arbesman and his associates[1] studied eight patients in whom repeated constitutional reactions, incurred in the course of routine hyposensitization therapy, were prevented by a preliminary dose of 100 mg. of Pyribenzamine. They also observed one patient who could tolerate, without reaction, 50 per cent more allergen than formerly when a preliminary dose of Pyribenzamine was given. Fuchs et al[2] reported that 50 mg. of Pyribenzamine, administered prior to the injection of pollen antigen, made possible greater dosage increases of pollen extract in twenty-six cases, and that their patients were able to reach a maximum dosage almost twice the amount they usually tolerated when taking the pollen extract alone. Green[3] found effective, in permitting the administration of larger amounts of antigen, 25 mg. of Pyribenzamine, administered prior to pollen therapy in hypersensitive patients, and observed no constitutional reactions when the effect of the antihistaminic agent had been dissipated.

The purpose of this paper is to present a new concept in pollen therapy. It essentially embodies the administration of large, rapidly increasing hyposensitization doses of pollen antigen, made possible by a twenty-four-hour simultaneous administration orally of a suitable antihistaminic preparation with each injection. The integration of these two therapeutic measures decidedly shortens the length of treatment in pollen allergy, decreases the number of injections, safely allows the administration of larger individual doses and more adequate total amounts of pollen antigen, and produces more uniformly satisfactory results.

RATIONALE OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY

Massive doses of pollen antigen, such as are about to be described, ordinarily would likely precipitate a severe constitutional reaction. However, a patient, protected with an antihistaminic agent, can tolerate repeatedly large, progressively increasing, provocative or shock doses of pollen antigen. From clinical results obtained in our study of a limited number of

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private patients, it appears that antihistaminic preparations "inactivate or neutralize" some "general-reaction-producing-substance," probably closely allied to histamine or H-substance, released locally by the excessive dose of antigen, which, without effective antihistaminic protection, would seriously shock the patient. Antihistaminic medication, administered in adequate amounts, exerts a prophylactic influence against the anticipated constitutional reaction of a deliberate overdose of pollen antigen. It further appears that the "inactivation or neutralization" of this "general-reaction-producing substance" by antihistaminic agents does not inhibit the formation of protective or blocking antibodies.

POLLEN DOSAGE SCHEDULE

Preseasonal and coseasonal pollen dosage schedules, which were both practical and rapid, were formulated. A maintenance schedule, designed to preclude subsequent preseasonal or coseasonal therapy, was also devised for perennial treatment. The doses were further arranged according to weight —for patients 100 pounds and over and for those under 100 pounds. The dose of the pollen extract, with its anticipated local release of a "general-reaction-producing substance." was governed not by the degree of response of the patient but by the amount of antihistaminic medication ("inactivating or protective" agent) which, in turn, depended upon the patient's weight.

The pollen unit dose employed in developing the schedule was the Coca-Noon Pollen Unit (0.00001 mg. of total nitrogen). In treating our patients, the allergenic extracts* of mixed grasses (20,000 pollen units per c.c., composed of equal parts of the pollens of June grass, orchard grass, sweet vernal grass, redtop, and timothy) and ragweed combined (20,000 pollen units per c.c., composed of equal parts of the pollens of common and giant ragweeds) were employed. Fresh extract was obtained every two to four weeks and was administered well in advance of the expiration date.

The pollen dosage schedule has been formulated for Boston, Massachusetts, and surrounding communities where the grass season of the most common and principal offenders (June grass, orchard grass, sweet vernal grass, redtop, and timothy) approximately extends from May 15 to July 15 and the ragweed season from about August 15 to September 20 or October 1. However, during the 1948 season in the Boston area, the grass season extended into September and ragweed pollen was still in the air up to November 15. The pollen dosage schedule, with slight variations in timing, can easily be employed in other sections of the country.

Preseasonal Schedule.—The preseasonal schedule (Table I) consists of eight rapidly increasing doses of pollen antigen which are arranged according to the weight of the patient. Those 100 pounds or over received a

*Prepared by the Lederle Laboratories, Pearl River, N. Y.

TABLE I. POLLEN DOSAGE SCHEDULE

Visit	Preseasonal		Coseasonal		Perennial	
	Patients 100 pounds and over	Patients under 100 pounds	Patients 100 pounds and over	Patients under 100 pounds	Patients 100 pounds and over	Patients under 100 pounds
1	250 PU	125 PU	125 PU	65 PU		
2	500 PU	250 PU	250 PU	125 PU		
3	1,250 PU	625 PU	625 PU	310 PU	20,000 PU bimonthly 6 injections per year.	10,000 PU bimonthly. 6 injections per year.
4	3,000 PU	1,500 PU	1,500 PU	750 PU		
5	6,000 PU	3,000 PU	3,000 PU	1,500 PU		
6	10,000 PU	5,000 PU	5,000 PU	2,500 PU		
7	15,000 PU	7,500 PU	7,500 PU	3,750 PU		
8	20,000 PU	10,000 PU	10,000 PU	5,000 PU		
Total	56,000 PU	28,000 PU	28,000 PU	14,000 PU	120,000 PU	60,000 PU

preseasonal total of 56,000 Coca-Noon Pollen Units (250, 500, 1,250, 3,000, 6,000, 10,000, 15,000, and 20,000); while patients under 100 pounds were given a preseasonal total of 28,000 units (125, 250, 625, 1,500, 3,000, 5,000, 7,500, and 10,000).

Preseasonal treatment was instituted at any time. Hyposensitization injections were given monthly, biweekly, weekly, or semiweekly. For each patient, the schedule of injections was predetermined, in order that the eighth dose would be administered just prior to the inception of the pollen season. There were thirty-seven patients on preseasonal ragweed therapy; fourteen received injections monthly, five biweekly, seventeen weekly, and one semiweekly. Six of these thirty-seven patients were simultaneously receiving coseasonal grass treatments also.

Coseasonal Schedule.—The coseasonal schedule (Table I) consists of eight progressively increasing doses of pollen antigen. Injections were administered weekly. Patients 100 pounds and over received a total of 28,000 Coca-Noon Pollen Units in divided doses (125, 250, 625, 1,500, 3,000, 5,000, 7,500, and 10,000 units); those under 100 pounds were given a total of 14,000 units (65, 125, 310, 750, 1,500, 2,500, 3,750, and 5,000). Fourteen patients received coseasonal therapy; four ragweed and ten grass. Six of the latter simultaneously received preseasonal ragweed injections also.

If the pollen season is longer than eight weeks, the eighth dose can be repeated weekly until the season ends. With a shorter season, as many coseasonal weekly injections as possible should be administered, the balance of the schedule then can be completed postseasonally and merged into the maintenance phase of specific pollen therapy.

When preseasonal therapy was instituted late, the preseasonal schedule of doses was administered until the specific season began, at which time the pollen unit dose was switched to a corresponding level in the coseasonal schedule. Injections were administered weekly until the top coseasonal dose was attained. The latter was continued weekly until the season ended.

Perennial Schedule.—The perennial schedule (Table I) extends from the end of one season to the beginning of the next and is continued for several years. It consists of the administration of top pollen doses at bimonthly intervals beginning with the month immediately following the

TABLE II. DISTRIBUTION OF ANTIHISTAMINIC DRUGS IN FORTY-FIVE CASES OF POLLEN SENSITIVITY

Antihistaminic Drug	No. of Pollen Cases	Grass	Ragweed	Combined Grass and Ragweed
Pyribenzamine Hydrochloride	5	1	3	1
Benadryl Hydrochloride	5		4	1
Histadyl Hydrochloride	5	2	3	
Thephorin	14	1	12	1
Neo-Antergan Maleate	6		4	2
Tagathen	3		3	
Decapryn Succinate	3		3	
Hydryllin	1			1
Thenylene Hydrochloride	1		1	
Neohetramine	2		2	
Total	45	4	35	6

season. The last (sixth) perennial dose should be given just before the next season begins. Thus, with six bimonthly injections given yearly, the need of subsequent preseasonal or coseasonal therapy is obviated.

The maintenance dose for patients 100 pounds and over is 20,000 Coca-Noon Pollen Units. This dose is injected bimonthly—a total administration of 120,000 units per year. The maintenance dose for those under 100 pounds is 10,000 pollen units given bimonthly—a yearly total of 60,000 units. Each year, the first and sixth doses should be respectively injected immediately after one season and before the next.

In all coseasonal patients, the coseasonal top dose was merged into the perennial schedule by one intermediate monthly injection. According to the patient's weight, the last coseasonal doses (eighth) were increased to 15,000 and 7,500 units the month immediately following the season. The next month they were increased to the top maintenance dose of the perennial schedule.

ADMINISTRATION OF ANTIHISTAMINIC DRUGS

In our study, the following antihistaminic drugs were employed: (1) Pyribenzamine Hydrochloride, (2) Benadryl Hydrochloride, (3) Histadyl Hydrochloride, (4) Thephorin, (5) Neo-Antergan Maleate, (6) Tagathen, (7) Decapryn Succinate, (8) Hydryllin, (9) Thenylene Hydrochloride, and (10) Neohetramine. Histadyl Hydrochloride and Thenylene Hydrochloride have the same chemical formula. These antihistaminic preparations were administered orally, in conjunction with hyposensitiza-

TABLE III. DOSAGE OF ANTIHISTAMINIC DRUGS

Antihistaminic Drug	Pre-injection Dose	1st Post-injection Dose	2nd Post-injection Dose*	3rd Post-injection Dose*	4th Post-injection Dose	5th Post-injection Dose	Total
Pyribenzamine Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Benadryl Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Histadyl Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Thephorin	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Neo-Antergan Maleate	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Tagathen	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Decapryn Succinate	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Hydryllin	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Thenylene Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Neohetramine	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.

*When the pollen antigen was administered late in the afternoon, the second and third post-injection doses were combined and given as a double dose at bedtime.

TABLE IV. ANTIHISTAMINIC ADMINISTRATION SCHEDULE

		20 minutes	1 hour	4 hours	4 hours		
	Pre-injection Double Dose of Anti-histaminic	Pollen Antigen Injection	1st Post-injection Double Dose of Anti-histaminic	2nd Post-injection Single Dose of Anti-histaminic	3rd Post-injection Single Dose of Anti-histaminic	4th Post-injection Single Dose of Anti-histaminic	5th Post-injection Single Dose of Anti-histaminic
Pollen antigen administered in the morning	9:40 a.m.	10 a.m.	11 a.m.	3 p.m.	7 p.m.	11 p.m.	7 a.m.
Pollen antigen administered in early afternoon	1:40 p.m.	2 p.m.	3 p.m.	7 p.m.	11 p.m.	7 a.m.	12 noon
Pollen antigen administered in late afternoon	5:40 p.m.	6 p.m.	7 p.m.	11 p.m. (2nd and 3rd post-injection doses combined)		7 a.m.	12 noon

tion therapy, to forty-five pollen-sensitive patients; four grass, thirty-five ragweed, and six combined (Table II). Throughout the study, the patients always received the antihistaminic drug originally allotted to them.

Both the individual doses and total twenty-four-hour administration were large—about two and one-half times the recommended amounts. Doses were given according to the patient's weight. Patients 100 pounds and over received doses as tabulated in Table III; those under 100 pounds received 50 per cent less.

Antihistaminics were administered prophylactically in such a manner that their effect lasted for about twenty-four hours (Table IV). A preliminary double dose (preinjection dose) was given twenty minutes prior to each injection of pollen antigen. One hour after the injection, the patient received another double dose (first postinjection dose). Thereafter, a single dose was administered every four or five hours for four doses (second, third, fourth, and fifth postinjection doses). When the pollen extract was given late in the afternoon, the second and third postinjection doses were combined and administered as a double dose at bedtime.

TABLE V. SIDE REACTIONS TO LARGE DOSES OF ANTIHISTAMINIC DRUGS DURING A TWENTY-FOUR-HOUR PERIOD

Patients coded by case number (Table VII).

Antihistaminic Drug	No. of Patients Receiving Anti-histaminic Drug	No. of Patients with Side Reactions	Drowsiness	Nausea	Dizziness	Numbness	Fatigue	Insomnia
Pyribenzamine Hydrochloride	5	4	18,27,36,39	18,27,36,39	39			
Benadryl Hydrochloride	5	4	30,31,35,37					
Histadyl Hydrochloride	5	4	19,23,26,40					
Thephorin	14	5	3, 7, 12, 17				17	25
Neo-Antergan Maleate	6	3	6, 8, 9					
Tagathen	3	3	32, 33, 34					
Decapryn Succinate	3	1	20			20		
Hydryllin	1	1	13					
Thenylene Hydrochloride	1	1	38	38	38			
Neohetramine	2	1	28					

In twenty-seven patients (60 per cent), side reactions were encountered to all the antihistaminic drugs employed (Table V). Despite the large doses, side effects were relatively mild and were never severe enough to warrant discontinuance of the drug. Drowsiness was the most frequent and prominent side effect. Nausea, dizziness, numbness, fatigue, and insomnia occasionally occurred also. In the majority of the cases, early side reactions either disappeared or were greatly diminished with continued administration.

CONSTITUTIONAL REACTIONS

As a prognosticator, the local reaction following the subcutaneous administration of pollen antigen was not dependable in foretelling the occurrence of a constitutional reaction. Mild, generalized symptoms were encountered with both small and extensive local reactions.

In our study of forty-five pollen-sensitive patients, seven patients (six preseasonal ragweed and one coseasonal grass) developed slight systemic symptoms. This represents seven constitutional reactions out of 360 treatment visits (1.6 per cent). There were no generalized reactions in the combined grass-ragweed sensitive patients. Sneezing, pruritus, urticaria, angioneurotic edema, and asthma were noted. These symptoms were delayed, occurring from one to twelve hours after the injection and lasted from a few minutes to four hours, being readily controlled with additional postinjection oral doses of an antihistaminic medication.

Whenever a constitutional reaction was encountered, however insignificant, the remaining pollen dosage schedule was reduced by 50 per cent. Despite this reduction, these exquisitely sensitive patients received in eight injections a total pollen dosage far in excess of the amount they could have tolerated without antihistaminic agents. After the specific season, begin-

TABLE VI. TWO YEAR COMPARISON OF PRESEASONAL RAGWEED TOTAL POLLEN DOSAGE IN NINE PATIENTS

Case No.	Weight	Age	1947 Total Pollen Dosage	1948 Total Pollen Dosage with Antihistaminic Integration	Times Pollen Units Increased	Antihistaminic Drug
2—B.N.	125 lbs.	50 yrs.	14,600 PU	56,000 PU	3.8	Thephorin
3—C.B.	170 lbs.	33 yrs.	4,100 PU	56,000 PU	13.6	Thephorin
4—H.W.	115 lbs.	27 yrs.	2,100 PU	56,000 PU	26.6	Thephorin
5—J.D.	65 lbs.	8 yrs.	9,145 PU	28,000 PU	3	Neo-Antergan
6—N.C.	130 lbs.	27 yrs.	12,000 PU	56,000 PU	4.7	Neo-Antergan
10—P.G.	135 lbs.	32 yrs.	10,800 PU	56,000 PU	5.1	Neo-Antergan
21—P.L.	130 lbs.	35 yrs.	2,850 PU	56,000 PU	19.6	Decapryn Succinate
22—L.L.	140 lbs.	34 yrs.	6,695 PU	56,000 PU	8.3	Decapryn Succinate
25—D.B.	120 lbs.	30 yrs.	10,250 PU	56,000 PU	5.4	Thephorin

ning with the first bimonthly perennial injection, the pollen dose was increased by 2,500 pollen units with each treatment until the top maintenance dose of 20,000 pollen units was attained. The latter was repeated bimonthly as suggested in the perennial schedule.

RESULTS

Forty-five pollen-sensitive patients (four grass, thirty-five ragweed, and six combined) from private practice received the combined hyposensitization-antihistaminic therapy. Injections were given subcutaneously in the arm. There were twenty-four females and twenty-one males. Forty-one patients were over 100 pounds; four were less than 100 pounds. Their ages ranged from eight to fifty-six years.

Clinical sensitivity was determined by the history and scratch tests performed with an extract of a 1-50 dilution. By skin tests, these patients had no associated sensitivities to foods, house dust, or moulds. Besides the six combined cases, eighteen of the thirty-five clinically sensitive ragweed patients also exhibited positive skin reactions to grass. These, however, lacked a positive clinical history, were considered "latent" cases, and did not receive grass hyposensitization therapy.

All the patients remained in the Greater Boston area during their specific season. None lived or were employed in air-conditioned establishments. All pursued their normal, daily routine. No medication was administered to the preseasonal cases during their specific season. The coseasonal patients received antihistaminic agents for twenty-four hours only with each weekly coseasonal pollen injection as per schedule.

Postseasonal serial testing of the skin and conjunctiva was not done. Results were based on the clinical course. Each patient kept his own clinical diary and carefully recorded the appearance and duration of any symptom. Results were tabulated as follows: 100 per cent, completely symptom-free; 95 per cent, a few sneezes accompanied with an insignificant and fleeting nasal obstruction; 75 per cent, slight symptoms lasting from two to four days during the height of the season; and 50 per cent slight to moder-

TABLE VII. RESULTS OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY IN FORTY-FIVE POLLEN SENSITIVE PATIENTS

Case No.	Age and Sex	Lbs.	Injections Given	Antihistaminic Drug	Total Coseasonal Grass PU	Total Coseasonal Ragweed PU	Total Preseasonal Ragweed PU	Total PU Given	Constitutional Reaction	Clinical Result
1 N.K.	47 F	165	monthly	Thephorin	0	0	38,500	38,500	1 with 10,000 PU dose	100%
2 B.N.	50 M	125	monthly	Thephorin	0	0	56,000	56,000	none	100%
3 C.B.	53 F	170	monthly	*Thephorin	0	0	56,000	56,000	none	100%
4 H.W.	27 M	115	monthly	Thephorin	0	0	56,000	56,000	none	100%
5 J.D.	8 M	65	monthly	Neo-Antergan	0	0	28,000	28,000	none	100%
6 N.C.	27 F	130	Grass weekly Ragweed monthly	*Neo-Antergan	28,000	0	56,000	84,000	none	100%
7 C.M.	36 M	170	Grass weekly Ragweed monthly	*Thephorin	28,000	0	56,000	84,000	none	100%
8 J.D.	37 M	170	monthly	*Neo-Antergan	0	0	56,000	56,000	none	100%
9 L.E.	33 F	140	monthly	*Neo-Antergan	0	0	56,000	56,000	none	100%
10 P.G.	32 F	135	monthly	Neo-Antergan	0	0	56,000	56,000	none	100%
11 W.K.	56 M	180	weekly	Thephorin	28,000	0	0	28,000	none	100%
12 J.M.	25 F	120	weekly	*Thephorin	0	0	29,000	29,000	1 with 1,250 PU dose	100%
13 D.M.	12 F	110	weekly	*Hydryllin	28,000	0	56,000	84,000	none	Grass 100% Ragweed 75%
14 E.W.	13 F	115	Grass weekly Ragweed monthly	Neo-Antergan	28,000	0	56,000	84,000	none	100%
15 F.A.	30 F	115	monthly	Thephorin	0	0	56,000	56,000	none	100%
16 M.L.	8 F	66	bi-weekly	Pyribenzamine	0	0	28,000	28,000	none	100%
17 H.C.	38 F	190	monthly	*Thephorin	0	0	56,000	56,000	none	100%
18 M.C.	10 M	88	bi-weekly	*Pyribenzamine	0	0	28,000	28,000	none	100%
19 D.V.	37 F	116	weekly	*Histadyl	0	0	56,000	56,000	none	100%
20 C.B.	34 M	195	bi-weekly	*Decapryn	0	0	29,000	29,000	1 with 1,250 PU dose	100%
21 P.L.	35 M	130	monthly	Decapryn	0	0	56,000	56,000	none	100%
22 E.L.	34 M	140	bi-weekly	Decapryn	0	0	56,000	56,000	none	100%
23 C.M.	13 F	103	weekly	*Histadyl	28,000	0	0	28,000	none	100%
24 R.B.	34 M	182	bi-weekly	Histadyl	0	0	56,000	56,000	none	100%
25 D.B.	30 F	120	weekly	*Thephorin	0	0	56,000	56,000	none	100%
26 M.P.	17 F	120	weekly	*Histadyl	28,000	0	0	28,000	none	100%
27 R.S.	26 M	130	weekly	*Pyribenzamine	28,000	0	56,000	84,000	none	Grass 95% Ragweed 50%
28 H.P.	29 M	210	weekly	*Neohetramine	0	0	28,375	28,375	1 with 500 PU dose	75%
29 M.H.	41 M	180	weekly	Neohetramine	0	0	56,000	56,000	none	50%
30 D.D.	15 M	137	weekly	*Benadryl	28,000	0	56,000	84,000	none	100%
31 K.C.	11 M	90	weekly	*Benadryl	0	0	28,000	28,000	none	100%
32 A.C.	39 F	150	weekly	*Tagathen	0	0	28,375	28,375	1 with 500 PU dose	100%

TABLE VII. RESULTS OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY IN FORTY-FIVE POLLEN SENSITIVE PATIENTS (Continued)

Case No	Age and Sex	Lbs	Injections Given	Antihistaminic Drug	Total Coseasonal Grass PU	Total Coseasonal Ragweed PU	Total Preseasonal Ragweed PU	Total PU Given	Constitutional Reaction	Clinical Result
33 R.D.	45 M	151	weekly	*Tagathen	0	0	56,000	56,000	none	100%
34 G.M.	23 F	167	weekly	*Tagathen	0	0	56,000	56,000	none	100%
35 J.M.	17 M	155	weekly	*Benadryl	0	0	56,000	56,000	none	100%
36 V.B.	25 F	102	weekly	*Pyribenzamine	19,250	0	0	19,250	1 with 5,000 PU dose	95%
37 F.M.	18 F	105	weekly	*Benadryl	0	0	56,000	56,000	none	100%
38 R.P.	35 F	121	weekly	*Thenylene	0	0	56,000	56,000	none	100%
39 J.R.	34 F	118	weekly	*Pyribenzamine	0	0	56,000	56,000	none	100%
40 M.D.	40 F	130	weekly	*Histadyl	0	0	56,000	56,000	none	100%
41 J.D.	56 M	230	semi-weekly	Benadryl	0	0	30,500	30,500	1 with 3,000 PU dose	75%
42 R.S.	37 M	115	weekly	Thephorin	0	28,000	0	28,000	none	100%
43 E.V.	26 F	130	weekly	Thephorin	0	28,000	0	28,000	none	100%
44 E.W.	31 M	192	weekly	Thephorin	0	28,000	0	28,000	none	100%
45 D.W.	32 F	125	weekly	Thephorin	0	28,000	0	28,000	none	100%

*Patient exhibited side reactions to antihistaminic drug.

ate symptoms of several hours duration appearing intermittently throughout half the season and being more pronounced at the season's height.

Tolerance of Massive Pollen Doses.—The combined hyposensitization-antihistaminic technique safely allowed the administration of large doses of pollen antigen. The individual total amounts of ragweed pollen units injected preseasonally to nine patients, treated in 1947 without antihistaminic integration and in 1948 with antihistaminic preparations, were compared (Table VI). In 1947, these exquisitely sensitive patients tolerated small individual doses only and allowed a small dosage increase with each injection. Large increases produced systemic symptoms. Postseasonally, during 1947-1948, they were treated perennially and received their maximum dose at monthly intervals. However, preseasonally in 1948, when effectively protected with antihistaminic agents, they were able to tolerate from three to twenty-six times more pollen antigen without any untoward result.

Preseasonal Treatment.—Preseasonal ragweed therapy was administered to thirty-seven patients (Table VII). Six of these simultaneously received coseasonal grass injections also. Twenty-seven patients, over 100 pounds in weight, tolerated the scheduled doses of pollen antigen and each received, in eight injections, a preseasonal total of 56,000 pollen units of

ragweed. Four patients, under 100 pounds, completed their schedule and individually received a total of 28,000 pollen units in eight divided doses. The remaining six patients, Cases 1, 12, 20, 28, 32, and 41, all over 100 pounds, exhibited an exquisite sensitivity and developed mild constitutional symptoms with 10,000, 1,250, 1,250, 500, 500, and 3,000 pollen unit doses, respectively. As a result, the remainder of their schedule was decreased 50 per cent. Each received a total pollen dosage in excess of 28,000 pollen units.

All of the thirty-seven ragweed-sensitive patients had gratifying results. Thirty-two patients were adequately protected and had a 100 per cent result; three had 75 per cent; and two had 50 per cent. The latter were most enthusiastic because the improvement experienced represented the best result ever obtained.

Coseasonal Treatment.—There were fourteen patients, all over 100 pounds, who received coseasonal therapy; four ragweed and ten grass (Table VII). Six grass-sensitive patients concomitantly received preseasonal ragweed injections also. Thirteen patients completed their schedule and each received 28,000 pollen units in eight injections. The remaining patient, Case 36, developed a mild constitutional reaction with the 5,000 pollen unit dose and, because the remaining doses were reduced 50 per cent, received a total of 19,250 pollen units.

Twelve patients (eight grass and four ragweed) had a 100 per cent result. Two grass cases claimed excellent results (95 per cent). One patient, Case 27, had mild hay fever for one day lasting for a few hours while picnicking on the shores of a lake. The other patient, Case 36, sneezed occasionally during the early days of treatment.

SUMMARY AND CONCLUSIONS

Hyposensitization therapy and antihistaminic preparations have been integrated in such a manner as to present a new concept in the treatment of pollen allergy. The combined hyposensitization-antihistaminic technique enabled forty-five pollen-sensitive patients to tolerate safely massive doses of pollen antigen. They thereby attained a large total pollen dosage and the optimum single dose level within a relatively short time and with a substantial decrease in the number of required injections. The large pollen dosage conferred a tremendous degree of protection, heretofore not always obtainable, to all the patients during their specific season.

REFERENCES

1. Arbesman, C. E.; Koepf, G. F., and Lenzner, A. R.: Clinical studies with N'pyridyl, N'benzyl, dimethylethylenediamine monohydrochloride (Pyribenzamine). J. Allergy, 17:275-283, 1946.
2. Fuchs, A. M.; Schulman, P. M., and Strauss, M. B.: Clinical studies with Pyribenzamine (N'pyridil-N'benzyl-dimethylethylenediamine) in hay fever. J. Allergy, 18:385-390, 1947.
3. Green, M. A.: Letters, Internat. Correspondence Soc. Allergists, 10:100, 1947.

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SIGNIFICANCE OF MEDIASTINAL SHIFT IN ASTHMA

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THERE ARE various abnormalities which may affect the mobility of the mediastinum. In a healthy state, the mediastinum is not fixed, being mobile during the respiratory cycle. The mobile mediastinum responds by shifting laterally to equalize differences in intrathoracic pressure as a result of unequal aeration to a portion of a lung. Recognition of pendular shifts of the mediastinum are important in detecting complications of bronchial asthma.

ETIOLOGY OF MEDIASTINAL DISPLACEMENTS

In a healthy state, the descent of the diaphragm causes narrowing, and the ascent widening, of the mediastinum. Lateral recumbency causes a shift of the mediastinum and its contents to the dependent position. The diaphragm, on the same side, moves upward as a result of increased pressure exerted by the abdominal organs. The mediastinum widens when one assumes the prone position.

Unequal pressure in the two sides of the chest or traction brought about by disease often causes mediastinal displacements. Such traction may involve a localized portion of the septum or may result in a total dislocation of the mediastinum and its contents.

A permanent shift of the mediastinum and its contents is frequently seen in unilateral fibrosing pleuropulmonary diseases. The gradual contraction of the diseased organ and the compensatory emphysema of the contralateral lung cause the mediastinum to be displaced to the affected side. In the presence of an expanding tumor or an aneurysm in the upper aperture of the thorax, the trachea may be pushed to the contralateral side. Unilateral pleural effusion is a common cause of mediastinal displacement. The displacement may be prevented or minimized by homolateral bronchial obstruction or fixation by a previous mediastinitis and pleuritis. Displacement of the mediastinum may result from a high dome of the diaphragm from causes such as eventration of the diaphragm, subphrenic abscess and gas collections, especially in the splenic flexure of the colon and in the stomach.

Displacements of the mediastinum are often seen in bronchial spasm and in partial and complete bronchial occlusion with atelectasis, many cases of which are associated with the bronchial asthmatic state. One of the cardinal features of bronchial asthma is a narrowing of the diameter of the bronchi, usually seen in the smaller bronchi but in many instances

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involving one or more of the larger bronchi. A partial or complete occlusion may occur. Therefore, in studying mediastinal shifts in the bronchial asthmatic patient, one must appreciate the many causes of bronchial obstruction:

Extrinsic.—Any extrabronchial disease which as a result of pressure on or invasion of the air passages might narrow or occlude the lumen of the tube.

Intrinsic.—Intrabronchial obstructions such as tenacious sputum, fibrinous casts, broncholiths, postoperative retention of secretions, foreign bodies, swelling of the mucosa, spasm, inflammatory stenosis, bronchogenic neoplasms, distortions of the lumen by some mechanical cause and congenital abnormalities should be considered.

It must be remembered that every wheezy chest is not necessarily a bronchial asthmatic chest and that any of the causes of mediastinal displacement might be the reason for the supposed asthmatic state.

PATHOLOGIC PHYSIOLOGY

The physiologic effects of tracheobronchial obstruction may be divided into their respiratory and their cardiovascular actions. An understanding of the manifestations of bronchial obstructions, especially as pertains to complications of bronchial asthma, is essential in determining the reason for a shifting mediastinum. Of major importance are the following: (1) the site of the obstruction, whether the lesion affects a single bronchus, several bronchi, or is diffuse; (2) the degree and character of the obstruction, whether partial or complete, simple or valvular, transient or permanent; (3) the time taken for the development of the obstruction; (4) the cause of the obstruction, whether within the lumen, in the submucosa or outside the bronchial wall; (5) the condition of the lung with respect to the presence of infection during the period of obstruction; and (6) the state of the pulmonary and systemic circulations.

The effects of bronchial obstruction are reflected not only in the affected bronchopulmonary segment but also in the uninvolved parts of both lungs, the circulatory system, the intrapleural pressure, and in practically all the contents of the thoracic cavity, depending on the factors previously mentioned.

In the presence of a slight degree of by-pass valve type obstruction, which does not interfere with the free inflow or outflow of air, no physiologic disturbances may be detectable. If it is of sufficient degree to interfere with free inflow and outflow of air, unequal intrapulmonary pressures may develop with a shifting mediastinum. Inasmuch as such obstructions are accentuated under stress, by periodic impaction of the lumen with secretion or by temporary swelling of the mucosa, the distal lung segment may undergo eventual changes.

In higher degrees of bronchial obstruction, in which a check-valve or ball-valve mechanism permits the inflow but prevents the outflow of air (Fig. 1), the bronchopulmonary segment distal to the site of obstruction becomes overinflated, since expiration is associated with reflex narrowing

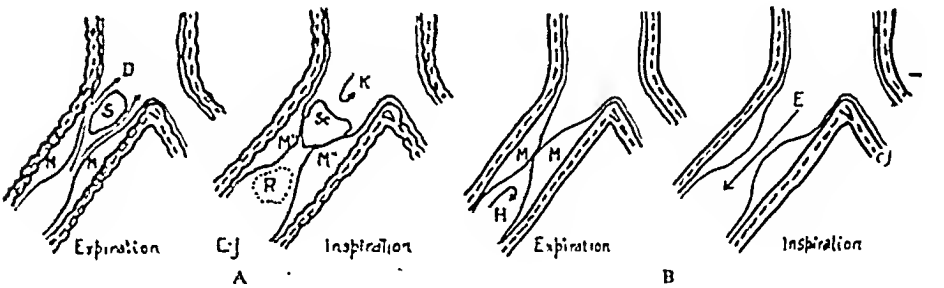

Fig. 1. (A) Mechanism of obstructive atelectasis produced by a small mass of secretion (S) acting like a check-valve in a pump. It rests in a valve seat of swollen bronchial mucosa at a bronchial orifice (M,M), but at each expiration it is lifted by the expiratory air current, allowing air to escape, as indicated by the darts (D). At the beginning of inspiration the suction pulls the mass (Se) down tightly in the valve seat, so that no air can enter (K). Repeated twenty-odd times per minute atelectasis results from pumping air out of the tributary area. A mass of secretion (R) below the inflammatory narrowing (M,M) would have the reverse effect of pumping air in, producing emphysema. Both these valvular mechanisms are seen every day in a busy bronchoscopic clinic. The resulting atelectasis or emphysema has been confirmed by physical signs and fluoroscopy.

(B) The expansile check-valve, which is the commonest form of valvular obstruction of the bronchi. The swollen mucosa (M,M) comes in contact at the start of the expiratory phase, preventing exit of air; but on inspiration, the enlargement of the bronchial diameter is sufficient to make a small opening for admission of air (E). Promptly at the beginning of the following expiratory phase the diminution of bronchial diameter promptly closes the narrowed lumen, trapping the air below the obstruction. Obstructive emphysema of the tributary area is the result. (Jackson and Jackson: Ear, Nose and Throat Diseases.)

of the bronchial lumen, causing the air to be trapped in the alveoli. This may become of sufficient degree to result in a shifting mediastinum. The condition gives rise to obstructive emphysema of varying degree and severity.

Complete obstruction, in which a stop-valve mechanism prevents the inflow as well as the outflow of air, causes atelectasis of the affected bronchopulmonary segment, the air trapped in the alveoli being absorbed by the capillaries within a few hours. Atelectasis may develop slowly or rapidly. There is a reduced lung volume in atelectasis and in any plugging or narrowing of a bronchus without atelectasis of sufficient degree to decrease inspiratory air in-take to a portion of lung. This serves to increase the normally negative intrapleural pressure. The mobile mediastinum shifts immediately to compensate for the loss of lung volume. The shift is toward the affected side on inspiration and, when severe enough, may remain displaced on full expiration. In the moderate to severe degrees of bronchial obstruction, the dome of the diaphragm is restricted in its downward motion and there is limitation of expansion of the hemithorax on the affected side. Additional compensation is affected by the distention of the uninvolved parts of both lungs. In obstructive emphysema, the lung volume increases in the tributary segment. When of sufficient degree, the medias-

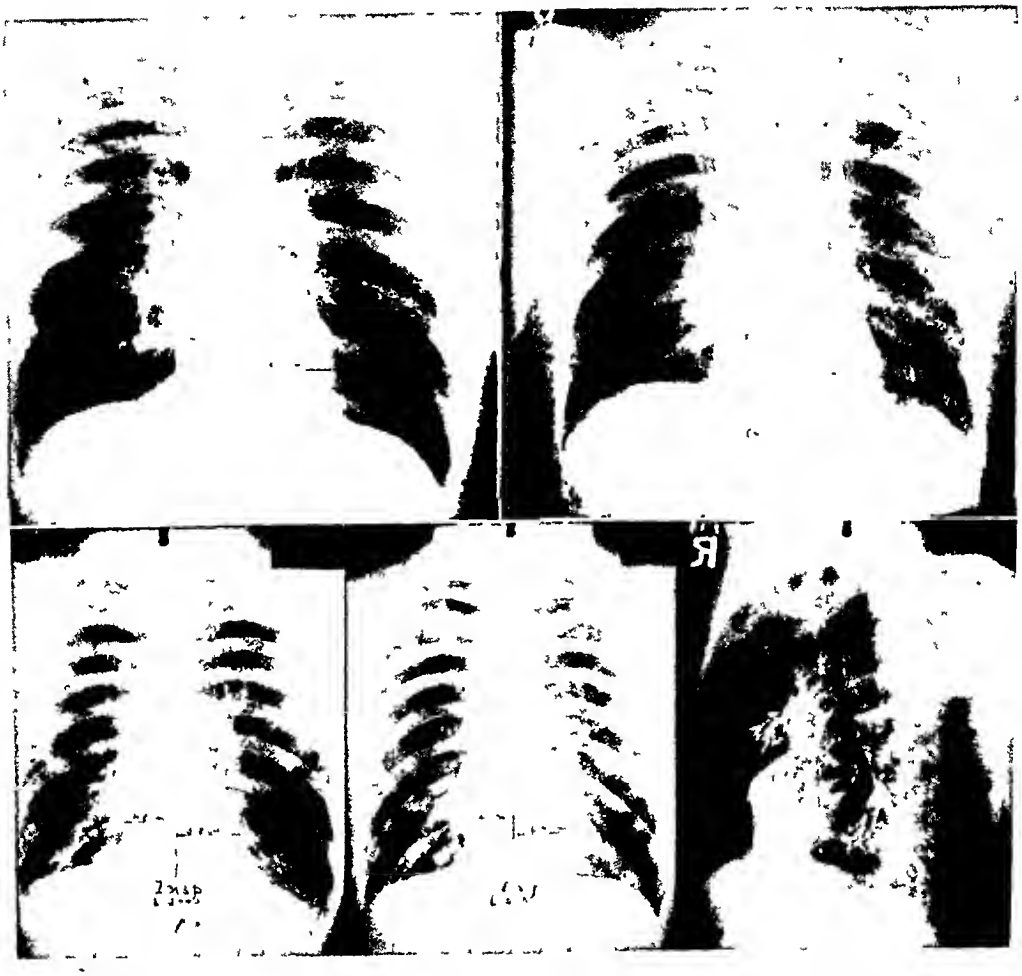

Fig 2. *(above)* Films made on full inspiration and full expiration in an allergic bronchial asthmatic with a mixed type of infection demonstrate a definite inspiratory shift of the heart to the right A more complete aeration is accomplished in the lower part of left lung on inspiration with a greater descent of the left dome of the diaphragm On expiration there is a corresponding lack of egress of air from the lower part of right lung These findings were due to mucus plugs in the lower right bronchial tree. All of the above findings disappeared soon after the plugs were removed.

Fig. 3. *(below)* The inspiratory and expiratory films of a chronic bronchial asthmatic with mixed type of infection demonstrate the inspiratory shift to the right more conclusively than the inspiratory film. Bronchogram (b) demonstrates stenotic narrowing of three branches of the right lower lobe and the right main stem bronchus and some cylindrical dilatation distally. All stenotic foci were subjected to repeated bronchoscopic dilatations with loss of mediastinal shift for some time, but bronchiectasis and abscess forced right middle and lower lobectomy.

tinum shifts toward the unaffected side in the expiratory phase and if severe enough may remain displaced on full inspiration. There is a limitation of upward motion of the dome of the diaphragm on the affected side and there is flattening of the dome and maintenance of an expanded hemithorax.

These compensatory physiologic changes are associated with phenomena which often result in permanent lung damage. In the bronchial asthmatic patient, the partial or complete bronchial occlusions due to spasm, edema, mucus plug or stenosis (Fig. 3) are the conditions which precede atelectasis, parenchymal inflammations, bronchiectasis, emphysema, pneumothorax and mediastinal emphysema.

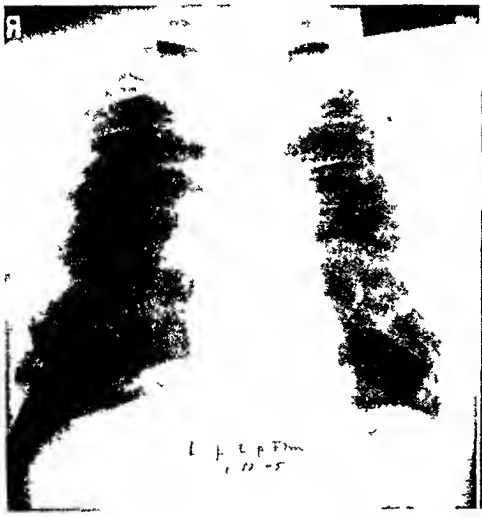

Fig 4 This is a double exposure film, one exposure on full inspiration and one on full expiration, which shows considerable inspiratory shift of the myocardial shadow to the left in an allergic bronchial asthmatic with a mixed type of infection This shift was due to mucopurulent plugs in left lower lobe bronchi and a small region of atelectasis in the lower part of left lung The mediastinal shift was absent a few days after bronchoscopy, but the atelectasis was slower in clearing

Fig. 5 Fluoroscopic observation and films made on inspiration and on expiration on a highly allergic bronchial asthmatic demonstrated an inspiratory shift of the heart to the left, which was found at bronchoscopy to be due to a mucus plug completely occluding a main branch of the lower left lobe bronchus A sharp interruption of the column of air is faintly visible (arrow). Several bronchial stenotic foci were found in the right perihilar region of increased density with retained secretions distally.

ROENTGENOLOGIC OBSERVATIONS

The roentgenologic findings are of great value in detecting mediastinal shift They are in keeping with the pathologic physiology as discussed. A conventional roentgenographic examination will not detect a shift unless it is marked Fluoroscopy is particularly revealing since one can detect a minor pendular shift of the mediastinum by observing the heart and/or occasionally the aortic arch during the respiratory cycle It may be recorded on two films, one made on full inspiration and the other on full expiration (Fig 2), or on a double exposure film, one exposure on full inspiration and the other on full expiration (Fig 4).

A pendular shift of the mediastinum may occur in an asthmatic bronchitis from any one of the several types of obstructive mechanisms An inspiratory shift of the mediastinum may occur when there is an accumulation of secretion above a focus of associated swelling of the mucosa (Fig 1, A), producing a check-valve obstruction on inspiration The inspiratory shift to the affected side is all that may be seen (Fig. 2), but if this mechanism is prolonged and of sufficient degree, then atelectasis in one of the various forms depending on the size and number of bronchi or bronchioles so involved, may become apparent. When larger areas of atelectasis occur, a shift of the mediastinum is usually apparent in the conventional film of the chest, but it may be seen more readily on the fluoroscopic screen and/or with one or both types of inspiratory and expiratory roentgenographic examinations (Figs. 3 and 4) A plug in a fair-sized

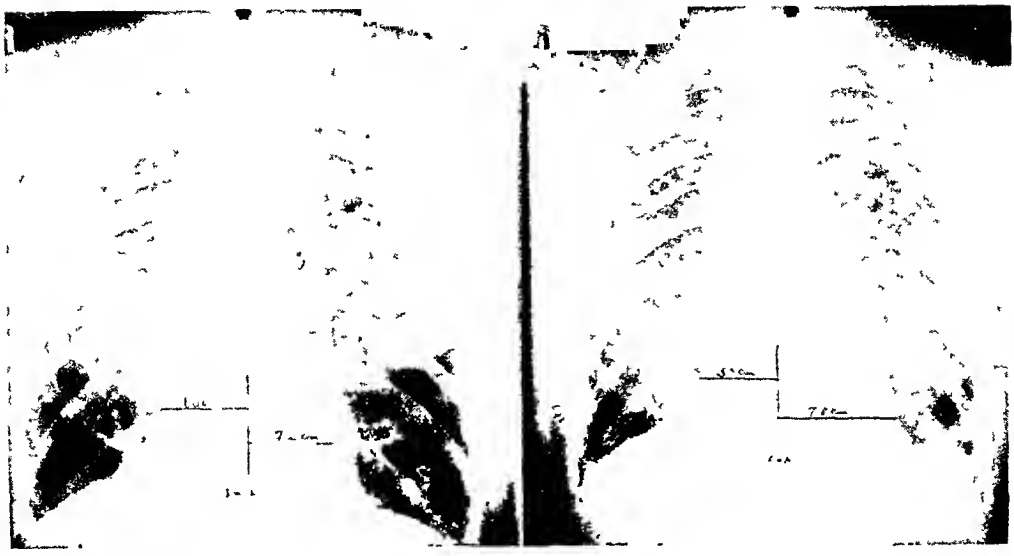

Fig. 6. Inspiratory and expiratory films of a chronic bronchial asthmatic with a mixed type of infection show emphysema at the bases and an inspiratory shift to the right. A chronic inflammatory constriction of the right lower lobe bronchus without any appreciable accumulation of secretion was dilated with known satisfactory state for two years.

bronchus without visible evidence of atelectasis distally may cause an inspiratory shift to that side even when there are several bronchostenoses with focal atelectasis in the opposite lung (Fig. 5). With the development of appreciable amounts of atelectasis, there appears a decreased range of motion of the diaphragm on the affected side with a higher dome on full inspiration. In the more pronounced atelectasis, a limitation of expansion of the hemithorax on the affected side becomes apparent.

There may be an accumulation of secretion below a focus of associated swelling of the mucosa (Fig. 1, R) producing a check-valve obstruction on expiration, or there may occur the expansile check-valve mechanism from a swollen mucosa coming in contact at the start of the expiratory phase, preventing exit of air; but on inspiration, the enlargement of the bronchial diameter is sufficient to make a small opening for admission of air (Fig. 1, B). With the development of emphysema, there develops an expiratory shift of the mediastinum to the unaffected side. When the emphysema is pronounced, it becomes apparent in the conventional film of the chest, but again the shift may be seen more readily on the fluoroscopic screen and/or with one or both types of inspiratory and expiratory roentgenographic examinations. With development of sufficient emphysema there appears a decreased range of motion and flattening of the diaphragm on the affected side with a lower dome on full expiration and maintenance of an expanded hemithorax.

Prickman and Moersch[67] have recently drawn attention to bronchostenosis as a common complication in either allergic or infectious asthma. The same pathologic physiology and the same roentgenologic findings pertain to bronchostenosis as are present in the bronchial asthmatic patient

with swollen membrane of a bronchus and a bolus of secretion above or below the point of stricture (Fig. 1, A, B). Bronchostenosis without secretion to produce a valve-like obstruction or without atelectasis may produce the inspiratory shift to the affected side because of a by-pass valve obstruction. Frequently in such instances nothing will be apparent on the conventional roentgenologic examination to suggest such a possibility (Fig. 6).

In a severe bronchial spasm with severe degree of emphysema where motion of the diaphragm is almost negligible, the ascent with widening and the descent with narrowing of the mediastinum practically disappear. The overdistended lungs keep the mediastinum in a narrowed and elongated state. With reversal of the greater portion of the emphysema, the normal mobility of the mediastinum returns.

Depending on the intensity, duration, degree and type of bronchial and/or bronchiolar obstruction, the lung changes may vary from that of acute bullous emphysema in a portion of one or all of one or both lungs to that of a massive collapse. There may be areas of obstructive emphysema interspersed with areas of atelectasis. Pathologic change may be of such degree and extent in both lungs that intrapulmonary pressure is equalized in each lung, so that there will be no mediastinal shift.

CLINICAL OBSERVATIONS

If any progress is to be made in reversing early stages of bronchial occlusion by bronchoscopic dilatations and bronchodilating drugs, it is believed that adequate roentgenologic study, which includes fluoroscopy and inspiratory and expiratory films, is absolutely essential. Detection of a mediastinal shift in the acute bronchial asthmatic state calls for adequate allergic management and repeated roentgenologic observations. If the mediastinal shift disappears, it may be assumed to have been due to a mucus plug. If it persists, bronchoscopic examination is indicated. Plugged bronchioles and occasionally a bronchostenosis may be found so that the bronchosocopist may be directed to it for bronchodilatations.

Symptomatically, there are features characteristic of bronchostenosis. There is often a severe persistent cough which fails to raise sputum and suddenly sputum may be profuse. The sputum is usually mucopurulent and often streaked with blood. Perhaps the most significant symptom of bronchostenosis is recurrent febrile episodes with or without preceding chills. This reaction may be very short or long in duration. Thus a history of frequent attacks of pneumonia is often obtained. The physical signs are very confusing and unreliable. In some instances they simulate the signs of a foreign body. There is usually a localized area of suppression of breath sounds.

In mediastinal shift with a history suggestive of bronchostenosis, immediate bronchoscopy and/or bronchography are indicated for diagnosis

and institution of proper treatment to aid in preventing or halting the progression of complications. An irreversible bronchostenosis is apparently an indication for thoracic surgery.

SUMMARY

The etiology and pathologic physiology of mediastinal displacements with special attention to the bronchial occlusion of the bronchial asthmatic patient are discussed. The roentgenologic observation of mediastinal shift by fluoroscopy and by inspiratory and expiratory films is stressed as essential in detecting, evaluating and treating the complications of bronchial asthma.

REFERENCES

1. Holinger, P., and Andrews, A. H. Jr.: Bronchial obstruction. Am J. Surg., 54:193, 1941.
2. Jackson, C., and Jackson, C. L.: Diseases of the Nose and Throat and Ear, including Bronchoscopy and Esophagoscopy. Philadelphia: W. B. Saunders Company, 1945.
3. Mansmann, James A., and Osmond, Leslie H.: Complications of bronchial asthma and their association with bronchostenosis. Pennsylvania M. J., 49:513, 1946.
4. Prickman, L. E., and Moersch, H. J.: Asthma and its association with bronchostenosis. M. Clin. North America, 23:961, 1939.
5. Prickman, L. E., and Moersch, H. J.: Bronchostenosis complicating allergic and infectious asthma. Ann. Int. Med., 14:387, 1940.
6. Rigler, Leo G.: The Chest. Chicago: The Year Book Publishers, Inc., 1946.
7. Rubin, Morris, and Rubin, Elis, H.: Diseases of the Chest. Philadelphia: W. B. Saunders Company, 1947.
8. Westermark, N.: On bronchostenosis: A roentgenological study. Acta radiol., 19:285, 1938.

AEROSOLS

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variables are in our present technique of antibiotic therapy than are desirable. The delivery of the nebulizer should be studied with a view to standardizing lung absorption and lung permeability. The inspiration time rather than the total time of administration was concluded to be of importance. An inspiration-time meter was devised and will be described in a following communication.

REFERENCES

1. Abramson, H. A.: Present status of aerosol therapy of the lungs and bronchi. *In* Progress in Allergy, edited by P. Kallos. Basel-New York: Karger, 1948.
2. Abramson, H. A.: Principles and practice of aerosol therapy of the lungs and bronchi. Ann Allergy, 4:440, 1946.
3. Abramson, H. A.; Reiter, C.; Sklarofsky, B., and Gettner, H. H.: Standardization procedure for determination of aerosol delivery of nebulizers by phenolsulfonphthalein aerosols. Ann Allergy, (in press).
4. Hufferd, R. W.: Penicillin aerosol: contribution of the Chemical Warfare Service to medicine. Science, 104:496, 1946.

SKIN SENSITIZATION TO BAL OINTMENT

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ONE OF THE great medical discoveries of World War II was the development of BAL (British Anti-Lewisite; 2, 3-Dimercaptopropanol) by Stockton and Thompson in R. A. Peters laboratory at Oxford, England.[1] It was developed by the British as a decontaminating agent and as an antidote for arsenical gas burns (Lewisite).[7] As an ointment it was used to prevent damage to the skin and eyes on exposure to Lewisite and vesicant gases. The above scientists proposed the theory that agents which "tie up" the SH (sulfhydryl) groups of tissues will interfere with cellular metabolism and tissue respiration.[7] BAL presumably exerts its beneficial effect by its selective affinity for certain metals, forming relatively stable, nontoxic and excretable compounds, thus preventing them from combining with the SH groups to produce toxic effects.[2]

Recent investigators have found BAL in a solution of peanut oil and benzyl benzoate to be a valuable and sometimes life saving drug in the treatment of systemic reactions, particularly from arsenic,[1] mercury[3,5] and gold.[6] This drug, however, is not without sensitizing potential and is capable of producing cutaneous allergic sensitization.[9] Many drugs of great therapeutic value are relatively harmless when used in the dosages recommended under controlled conditions for specific purposes, but may demonstrate marked sensitizing capacities when used indiscriminately and unwarrantedly.

The purpose of this report is to present five cases in which there was needless skin sensitization by such indiscriminate use. All of these patients had previous skin damage resulting from burns. Three had first degree burns and two second degree burns. The patients were wives of former servicemen who had been given the ointment with instructions as to its use and value in the event of Lewisite or arsenical vesicant gas burns. In each case BAL ointment was applied to the burned areas through an erroneous interpretation of its specific use.

SENSITIZATION OF DAMAGED SKIN TO BAL OINTMENT

During the years 1947 and 1948, five patients with papulo-urticarial lesions, surrounding erythema and edema came to the clinic with a tentative diagnosis of allergic dermatosis. The specific etiology was unknown and the type of sensitization was difficult to classify, as it differed from the eczematous contact type and the classical urticarial type. There was a lack of dissemination frequently seen in the eczematous type of sensitization with a complete absence of vesicles. In contrast to the typical urticarial

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type, scratch tests with BAL ointment in these cases revealed only mild to moderate erythema with no wheal formation.

The subjects suffered previous skin damage as a result of burns while cooking at home. A careful history revealed that the patients had applied an ointment to the burned areas from three to five times a day for six to thirteen days with a hope of hastening the healing process or preventing a progression of the skin damage. As stated previously the ointment was applied through a mistaken idea concerning its use. All patients were ambulatory and were requested to bring the ointment used to the clinic. It was later identified as 5 per cent BAL ointment.

Case 1.—A. J., a woman, aged twenty-two, was seen on June 4, 1947. She presented a healing first-degree burn on the left forearm with surrounding papulo-urticarial lesions accompanied by erythema and mild edema. The burned area, approximately 2 by 4 cm. was produced by spilling hot water on the arm when attempting to remove a pan of water from a stove six days previously. The patient stated that she applied an ointment (later proven to be 5 per cent BAL ointment) over the area three times a day until seen in our clinic. She was referred to the clinic because of the papulo-urticarial lesions with edema, pruritus, burning sensation and insomnia at night. The ointment was discontinued and the patient was given Benadryl, 50 mg. three times daily, phenobarbital, gr. 1½ at bed time, and ephedrine sulfate, gr. ⅜ three times daily. The lesions disappeared within five days; however, a brownish pigmentation remained at the periphery of the healed lesion for approximately four months.

Case 2.—O. B., a woman, aged thirty-one, was admitted to the clinic on July 3, 1947, with papulo-urticarial lesions on the terminal phalanx of the index and middle finger of the right hand with surrounding erythema and a burning sensation of two days' duration. Similar lesions with erythema and edema of three days' duration were observed on the left forearm. The patient gave a history of sustaining a first-degree burn by hot grease on the left forearm eight days before, and she had applied an ointment to the area with the fingers of the right hand. She stated further that she had experienced a similar burn on the left thigh by overturning a cup of hot water two weeks previously, to which she applied ointment from the same tube used in the present home treatment. The left thigh now presented small papulo-urticarial lesions with marked pigmentation at the periphery. There was intense pruritus in the thigh area which had been subjected to frequent scratching according to the patient. The lesions displayed marked improvement within three days after the discontinuance of the ointment and the use of ephedrine and Benadryl orally three times a day and phenobarbital at night.

Case 3.—A. C., a woman, aged twenty-two, was seen for the first time in the clinic on January 8, 1948. She presented confluent papulo-urticarial lesions (4 by 5 cm.) on the right thigh in the area of a healed first-degree burn resulting from an overturned pan of hot water ten days previously. There was also angioneurotic edema of the left eyelids and the left lateral aspect of the upper lip. The patient stated that she applied a "burn" ointment from a tube to the lesion on the right leg four to five times a day. She suffered from coryza during this period and frequently rubbed the left nostril and left eye with the hand which was used to apply the ointment. The patient admitted a continuance in the use of the ointment even though there was increased burning after each application following the fifth day. The

lesions cleared completely within six days after giving epinephrine subcutaneously, Benadryl orally and discontinuing the ointment.

Case 4.—D. G., a woman, aged twenty-six, was admitted to the clinic on February 12, 1948, at which time she presented a second-degree burn with an area of 3 by 6 cm. on the right forearm sustained by striking the arm against a hot iron. She applied an ointment (later determined to be 5 per cent BAL ointment) to the damaged area three to five times a day for nine days. The lesion did not heal but became progressively worse, with marked edema and intense pruritus. Scattered papulo-urticarial lesions formed at the periphery. The burned area was cleansed and a vaseline gauze dressing applied. Epinephrine was given subcutaneously, Benadryl and phenobarbital orally. The BAL ointment was discontinued and striking improvement was noted within three days. The lesions disappeared completely within twelve days.

Case 5.—A. C., a woman, aged thirty-four, was referred to the clinic on December 2, 1948, because of papulo-urticarial lesions surrounding a second-degree burn of the left wrist, with symptoms of burning and itching in and immediately surrounding the burned area. The inner aspect of the left thigh also presented an area, approximately 3 by 6 cm., with erythema, papules, mottling and edema. The injury to the wrist, 2 by 7 cm., was sustained by overturning a cup of hot coffee fourteen days before admission. The patient admitted that the damaged skin area of the left thigh was the site of injury by hot water two months previously. An ointment was applied three to four times daily to the wrist area for thirteen days and to the thigh area for six days before admission to the clinic because of marked pruritus without apparent benefit. However, the first-degree burn of the left thigh was treated in a similar manner for five successive days two months before without retardation of healing and a complete disappearance of symptoms. The ointment therapy (later identified as 5 per cent BAL ointment) was discontinued twenty-four hours before she was seen in the clinic because of nausea and a burning sensation in the mouth and around the eyes and nose. These symptoms evidently represent toxicity to the drug by rapid absorption as seen in cases of overdosage of the drug.[4]

DELIBERATE SENSITIZATION OF THE SKIN BY 5 PER CENT BAL OINTMENT

We were aware of the fact that the five patients discussed above were those with previous skin damage which possibly made sensitization less difficult. We wished to determine if 5 per cent BAL ointment would sensitize skin which was grossly normal if applied repeatedly. For this experiment we selected twelve patients who gave a negative history for allergic diseases. It was further determined that these patients had no previous exposure to BAL either in the form of an ointment, or a liquid. None of the patients showed evidence of skin damage resulting from burns, chemicals or physical trauma. Microscopically, the skin was obviously normal. Following a suggested procedure, as outlined by Sulzberger, Baer and Kanof, we attempted deliberate skin sensitization of the subjects.[10] Portions of the same BAL ointment used by the five patients with skin damaged by burns were applied by inunction in these twelve cases.

Procedure.—Each of twelve patients was instructed to rub gently a small amount (approximately 0.2 gram) of 5 per cent BAL ointment on the flexor surface of the left forearm two times a day. The approximate size

of the area selected for the repeated applications was 5 by 5 cm. We requested the patients to repeat the rubbing of a similar amount on the same area morning and night. They returned to the clinic at three-day intervals for observations and readings. If an eruption or marked erythema, which persisted for at least an hour appeared, they were instructed to discontinue the applications and report the same day for an inspection of the area and further recommendations. We regarded as positive sensitization only reactions of erythema which persisted with papulo-urticarial lesions.

Results.—Two cases showed evidence of sensitizations within twelve days.

The first case displayed marked persistent erythema on the afternoon of the fifth day, followed by confluent papulo-urticarial lesions on the sixth day. On the seventh day there was moderate edema extending approximately 4 cm. beyond the area of application.

The second sensitized case presented a moderate persistent erythema on the tenth day with numerous papulo-urticarial lesions on the twelveth day.

The remaining ten cases showed neither persistent erythema nor papulo-urticarial lesions after fifteen days of twice daily applications of the ointment. Patch tests with 5 per cent BAL ointment were made on the back of each patient before the beginning of the experiment. All were negative after forty-eight hours. These tests were repeated on the fifteenth day. The two subjects manifesting sensitivity to the ointment at the site of twice daily applications also presented positive patch tests on the fifteenth day. The morphological characteristics were similar to those resulting from inunction on the forearm. The patch test was negative in each of the ten cases with negative arm reactions.

Scratch tests on the twelve subjects revealed a mild erythema but no urticarial or wheal response. There was no apparent difference in the scratch tests response in the two sensitized subjects and the remaining ten non-sensitized subjects.

COMMENT

The type of sensitization in the five cases with previously damaged skin was somewhat difficult to detect because it differed from the accepted contact eczematous type and the classical urticarial type, yet possessing some features of both. None of these patients gave a history of previous sensitivity to drugs or previous allergic manifestations. Only on detailed questioning, the patient's description of the odor of the ointment used, and a subsequent check on the ointment brought to the clinic did we determine the allergenic agent in these cases.

There was evidence of a spread of sensitization in two of the five cases with burns as shown by erythema, edema and papulo-urticarial lesions at

distant points and postive patch tests on the back. The spread of sensitization was greater in those with previously damaged or burned skin areas than in those used in our control series with grossly normal skin. It is probable that the damaged tissue contained break down products consisting of large protein molecules which in combination with BAL molecules produced a drug-protein combination of relatively high sensitizing potential.

SUMMARY AND CONCLUSIONS

1. Five patients exhibiting first and second degree burns treated themselves with 5 per cent BAL ointment from six to thirteen days, with each presenting evidence of skin sensitization to the ointment. We have no way of knowing how many patients with similar skin damage treated themselves without evidence of skin sensitization.

2. All lesions of the sensitized skin were papulo-urticarial, with some erythema and occasional obvious edema, mottling of the skin, and increased pigmentation.

3. The lesions of sensitization dermatitis cleared on discontinuing the BAL ointment and using an antihistaminic and symptomatic therapy.

4. The lesions in the sensitized areas differed from the commonly accepted eczematous contact type and the standard urticarial type. Scratch tests were negative and patch tests displayed no vesicle formation.

5. The application of 5 per cent BAL ointment to grossly normal or undamaged skin of twelve subjects produced skin sensitization in two subjects. There was no history of allergic manifestations or previous exposure to BAL. The number of subjects sensitized is too small to establish a percentage incidence of sensitivity, but it does show that 5 per cent BAL ointment has a sensitizing capacity.

6. The relatively marked sensitizing potential of BAL ointment on damaged skin may be due to a combination of small BAL molecules with the proteins of injured tissue, forming a drug-protein combination of high antigenic quality.

7. Although BAL ointment proved to be a valuable drug during th recent war and has an important peacetime use for industrial arsenical poisoning, its power to sensitize must be kept in mind, especially if there is a history of its recent application to the skin and the lesions are papulo-urticarial in morphology with persistent erythema and edema.

REFERENCES

1. Eagle, Harry: The systemic treatment of arsenic poisoning with BAL (2, 3-dimercaptopropanol). J. Ven. Dis. Inform., 27:114, 1946.
2. Editorial: BAL in the treatment of arsenic and mercury poisoning. Ann. Int. Med., 25:986, 1946.
3. Gilman, A.; Allen, R. P.; Phillips, F. S., and St. John, E.: Clinical uses of 2, 3-dimercaptopropanol (BAL). X. The treatment of acute systemic mercury poisoning in experimental animals with BAL. J. Clin. Investigation, 25:5-49, 1946.

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HUNGARIAN MEDICAL TRADE UNION ASSOCIATION OF PHYSICIANS, SECTION OF ALLERGISTS

Abstracts of Lectures Presented at Second Meeting, June 2, 1948

MYCOTIC INFECTION AND ALLERGY AGAINST FUNGI IN THE PATHOMECHANISM OF INFANTILE ECZEMA

E. LIEBNER, M.D.

THE general conception of food allergy in the pathogenesis of infantile exudative eczema, as based upon positive egg-white reaction, positive complement reaction and Prausnitz-Kustner transference method, may be disputed as follows: (1) The skin-reaction is never eczematous. (2) It is never persistent, being positive in seborrheic dermatitis as well. (3) It is sometimes positive with varieties of eggs absent in the diet of mother and child. (4) Clinical symptoms rarely disappear or decrease with avoidance of the white of egg.

In 1938, Liebner succeeded in demonstrating fungi (varieties of oidia, trichophyton, epidermophyton, microsporon and molds) in twenty-one of thirty-seven cases of exudative eczema and seborrheic dermatitis; in 1947 in twenty-three of fifty-two cases of eczema; and in eighty-six of 109 cases of seborrheic dermatitis, corresponding with clinical characteristics known as microbiotic eczemata of adults; i.e., round, sharply outlined patches of centrifugal extension; scaling border, young efflorescences in the neighborhood and confluence into greater patches with serpiginous bordering with prevalently gluteal, perigenital and intertriginous localization of the first signs in areas predisposed for fungous infection. The appearance of lichenoid and eczematoid "ids" determines the polymorphism of symptoms and is to be explained by hypersensitivity. Patch-test with vaccines of oidia, pathogen fungi and molds gave positive eczematous reaction in eight of fourteen cases of exudative eczema; and in fourteen of thirty-one cases after several days it sometimes transformed into larger eczemata en plaque. The reaction was more prominent after scarification than on uninjured skin. No significant difference was found among the reaction of vaccines from oidia, pathogen fungi or mold. Sometimes positivity shows parallelism with appearance of "ids". Eosinophile cells may increase up to 15 to 32 per cent with lymphocytosis and leukopenia. Our investigations do not interfere with the question of pathogenesis in other cases devoid of demonstrable mycotic infection.

TUBERCULOUS ALLERGY AND BRONCHIAL ASTHMA

T. GLUCK

Bronchial asthma is a typical allergic disease. In most cases of asthmatic tuberculosis, allergy is demonstrable. Statistics of the author on the histories of asthmatics agree with the majority of research workers as follows:

(1) In approximately 15 per cent of the cases, hereditary tuberculosis

occurred. (2) 45 per cent of asthmatics had suffered from some mild form of tuberculosis (productive fibrous). The remaining 40 per cent of asthmatics derived their disease from various allergens, i.e., pollen, occupational disease, bacilli, toxins, et cetera. After complete recovery from mild tuberculosis, sooner or later, allergic conditions in the form of bronchial asthma may arise. Tuberculin had been introduced by Storm in 1926 in therapy of bronchial asthma. The majority of authors (Hajós, Kiss, Leibermeister) applied diluted tuberculin-solution (10^{-15}–10^{-5}). The author tried the same solution without success due to underdosage; therefore, he applied massive doses (0.01-0.03 gm.), after necessary precautions (blood analysis, history, x-ray, et cetera) and found that the association of fever raised the therapeutic effect of tuberculin. Sensitivity and asthmatic manifestations were reduced for months and even for years. No untoward effects of massive doses had been encountered. The author's experience, in accordance with that of others, seems to testify that, while allergic subjects resist serious tuberculous infection, the tuberculous organism does not incline to allergy.

DISCUSSION

L. Kiss: Kiss reports the effects of the tubercle bacillus as published earlier in special literature. In accordance with Gluck, he states that a great percentage of cases of bronchial asthma is based on tuberculous allergy. In opposition to Gluck's massive doses, he prefers caution, starting regular treatment with the limit-dosage of 1.10^{-15} gm., rising gradually in accordance with the method of Mantoux tests.

K. Hajos: Symptoms of past or present tuberculous infection were found in 21 per cent of asthmatics. Three and three-tenths per cent of cases of intrinsic asthma showed their first manifestation after tuberculous infection. Based on these findings, Gluck's view must be disputed, and tuberculin therapy used with caution. Tuberculin treatment cannot be mere fever-therapy, for which we have better-controlled methods. Tuberculin-treatment has its well-established indication and should be taken as specific desensitization, applying small doses. Fever-therapy in tuberculous patients may be dangerous.

PSYCHOSOMATIC ASPECTS OF BRONCHIAL ASTHMA

By K. HAJOS, M.D.

Psychosomatic relationships may be established by exact history-taking and detailed examination. Hence, in order to discover the psychic background, 1300 asthmatic patients were interrogated concerning the circumstances inducing the first asthmatic attacks. In 141 cases (11 per cent) the first attack followed nervous states, psychic excitement and depletion, while endocrine factors, with psychic and vegetative stimuli, caused the

Presented at the meeting of the Medical Association of Budapest, March 19, 1948.

first attacks in sixty-two cases. In 723 cases, the first attacks followed influenza, severe colds and infectious diseases. It is striking that during deprivations of wartime, such as bombing, deportation, and ghetto-life, the majority of asthmatic patients felt well, which is due to the diminished functioning of the entire autonomic nervous system, and of the psyche.

For our understanding, emphasis of the great importance of the psychosomatic relationship, as correctly applied, and not dogmatic psychotherapy, seems to be advisable. Persuasion, psychagogy, suggestion attached to breathing-exercises, and even psychoanalysis are rarely recommended.

Physical immuno-biological effects and psychotherapy must always be associated. The new therapeutic view unites different methods and excludes both one-sided immuno-biological or psychiatric theories. Allergic diseases can only be treated with knowledge and correct estimation of both somatic and psychic factors.

METHYL THIOURACIL TREATMENT OF BRONCHIAL ASTHMA

By MARY-KATHARINE HAJOS, M.D.

After correct estimation of history-taking, psychic and physical influence, effect of drugs, and clinical picture, seven asthmatic patients with hyperthyroidism had been treated with Basethyrin Richter (4-methylthiouracil). Treatment lasted for several months, and gave satisfactory results in relieving both symptoms with the minimum of side-effects. No allergic reactions to the drug were noted. Generally, Basethyrin alone was sufficient in treatment, but in severe congestion, combined strophantine and theophylline therapy increased the effect of both.

Presented at the Scientific Meeting of the Apponyi Policlinic, March 5, 1948.

TESTING FOR IDENTITY AND PURITY OF POLLEN EXTRACTS

(Continued from Page 755)

REFERENCES

1. Ellis and Dahl: Concerning the reliability and unreliability of dried pollen from commercial sources. J. Allergy, 18:55, 1947.
2. Veldee, M. V. (editor): Specifications recommended as guides in the collection and preservation of pollens. Ann. Allergy, 6:56, 1948.
3. Wodehouse, R. P.: Timothy versus Bermuda grass. Ann. Allergy, 5:137, 1947.
4. Wodehouse, R. P.: Patterns of allergic sensitization. Ann. Allergy, 6:538, 1948.
5. Wodehouse, R. P.: The origin of patterns of allergic sensitization. Ann. Allergy, 6:172, 1949

HUNGARIAN MEDICAL TRADE UNION, SECTION OF ALLERGISTS OF THE SECTION FOR CLINICAL MEDICINE

Abstracts of Lectures Presented Centennial Week, September 4-12, 1948

ALLERGIC RELATIONSHIPS OF DISEASES OF THE ALIMENTARY TRACT

PROF. DR. B. FORNET

ALLERGIC origin in gastritis may be proved by clinical symptoms appearing after allergen administration, hyperergic response of the mucosa, and presence of eosinophile cells. Generalized symptoms may appear in other organs. Desensitization and adrenaline give good results in treatment; cutaneous tests are positive.

Gastric ulcers of allergic origin are based on inherited disposition. Eosinophile cells and Charcot-Leyden's crystals in colica mucosa, recovery after ulcerative colitis from shock therapy, acute gastritis elicited by otherwise nontoxic agents, prove allergic origin. Occasional alimentary intolerance, allergic salvarsan and atophan toxicoses elicit allergic hepatitis. Anaphylactic experiments prove occurrence of allergic pancreatitis and pancreas necrosis. Pathologic permeability of the digestive mucosa and infectious enterocolitis may lead to allergic manifestations of other organs. Deficiency diseases may improve allergic complaints.

CONTRIBUTIONS TO CHEMICAL INCITEMENT THEORY IN HYPERSENSITIVENESS

PROF. DR. I. WENT

Biologically active substances creating anaphylactic symptoms may elicit anaphylactic phenomena after primary stimulation of various tissue-cells. Reduction of histamine sensitiveness by repeated histamine injections failed to increase histamine tolerance. Introduction of antihistamines proved to be inefficient. Biologically and pharmacologically active substances linked with protein molecules produce antisera, inhibiting the active group; thus increasing histamine tolerance by means of immunization. Treatment with histamine antigen (histamine-azobenzol-azoprotein, synthetized in 1942) protected experimental animals from toxic histamine doses and experimental anaphylaxis.

PHYSICAL ALLERGODERMATOSES

PROF. DR. E. RAJKA

Differential diagnosis of allergic skin manifestations elicited by physical agents and by chemical allergens are as follows:

Mechanical agents and light act externally alone; thermical agents have

internal effect as well. The physical agent reaches the stratum papillare of the intact skin; the reagin is linked to H-substances. Thermical agents may cause sharp-limited inflammation with additional distal effect via the lymphatic and blood streams. Passive transfer, in association with other allergic criteria, causes the allergo-physical process of fixed reagins.

ACQUIRED SENSITIZATION OF LIVER EXTRACTS

DR. G. GORTVAI

Allergic reactions of parenteral liver-therapy are rarely severe. Individual specific desensitization following history and intracutaneous tests, is advisable. In case of protracted desensitization, folic acid treatment should be encouraged. Passive transfer proves presence of reagins in hypersensitiveness. Since 1933, two cases out of forty-seven developed severe allergic reactions; seven of a milder degree.

RELATIONSHIPS OF ALLERGIC PAROXYSMS IN THE FEMALE SEX CYCLE

PROF. DR. K. HAJOS

Auto-endogenous hormone-sensitiveness may cause allergic symptoms associated with changes of hormone level and external hormone administration. Hetero-endogenous hormones may act as allergens.

Endocrine changes associated with the female sex cycle depend on allergic disposition and constitution, eliciting allergic paroxysms. Allergic symptoms are influenced by changes in endocrine functions through neurohormonal control, via autonomic nervous centers. This influence lies in establishment, disappearance or modification of paroxysms. In several cases of periodical hormone secretion, x-ray castration, estrogenic substances and progesterone improved symptoms. Sometimes, however, allergic paroxysms were inhibited by elimination of the central nervous factors dominating endocrine balance with chloral hydrate and barbiturates.

Allergic symptoms of pregnancy are associated with sensitization of the maternal organism by endogenous proteins (chorion, fetus). Towards the end of pregnancy, histaminase level rises in the blood serum. Treatment with pregnant blood-serum improved allergic manifestations.

HORMONE ALLERGY

DR. M. K. HAJOS

Tests for hormone sensitiveness with estrogenic and androgenic hormones (progesterone, pregnanediol, estrone, testosterone, androsterone) were performed in 107 cases of various allergic diseases, thus proving presence of hormone allergy with normal endocrine functions, and calling attention to its influence on diagnosis and course of treatment.

Forty-five cases showed positive reactions. Out of three cases of keratitis rosacea two were sensitive to progesterone, one to androsterone.

Importance of the tests lies in definition of relationships of changes of endocrine functions and hormone levels. Cases of estrogenic and progesterone sensitiveness were treated successfully with specific desensitization.

ALLERGIC DISEASE OF THE HEART

DR. B. LASZLO

A great number of infectious diseases are based on allergic sensitization. Susceptibility of myocardium and blood vessels to allergic reactions may elicit benign allergic myocarditis, such as late myocarditis in scarlet fever, with inflammation of the bundle branches. Streptococcal infection, erysipelas, and various foci may have the same effect. As regards treatment, the antigen has to be eliminated. Anti-allergic drugs and antihistamines may have a favorable influence on allergic myocarditis. Only cases of myocarditis with allergic criteria, positive skin tests and allergic symptoms are of allergic origin.

DIABETIC DISPENSERS IN PREVENTION OF COMPLICATIONS

DR. D. SIMOR

Statistical details of 1943-1945-1948 enumerate the complaints and complications of taking patients to the dispenser. Allergic response to insulin has been considered. The importance of treatment of diabetics lies in prophylaxis of developing complications. Association of asthma and diabetes, skin diseases and diabetes, as well as insulin desensitization, has been controlled with special care.

AN EVALUATION OF NEO-ANTERGAN IN DERMATOLOGY

(Continued from Page 782)

4. Feinberg, S. M.: Histamine and antihistaminic agents. J.A.M.A., 132:702-703, (Nov. 23) 1946.

5. Hunter, R. B.: Neo-Antergan in the treatment of urticaria. Lancet, 1:672, 1947.

6. Last, M. R., and Loew, E. R.: Antihistaminic drugs and capillary activity. J. Pharm. & Exper. Therap., 89:81-91, (Jan.) 1947.

7. Loew, E. R.: Pharmacology of antihistaminic compounds. Physiol. Rev., 27:542-573, (Oct.) 1947.

8. Lowell, F. C.: The newer concept of allergy to drugs and bacteria. J.A.M.A., 136:665, (March 6) 1948.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

FOR THE SAKE OF UNIFORMITY

The manuscripts which pass over the editors' desks are gratifyingly uniform in their quality excepting for the occasionally very excellent and perhaps the rare not-up-to-standard paper. No two, however, are uniform in their use of abbreviations for units of measurement. Inches and centimeters, grains and grams often follow each other dizzily across the page to the despair of the editors, typesetters, proofreaders, and ultimate readers. Few authors have access to the Handbook of Chemistry and Physics. Since "order is Heaven's first law," it was deemed advisable to give this subject prominence by using the editorial page to list the abbreviations standardly used. Although the author is truly the final arbiter as to the units in which he wishes to describe his work, it would perhaps take little effort to bring papers on allergy into line with those in other fields of medicine and the physical and chemical sciences.

In measuring linearly, as for example, the diameter of a wheal, the standard abbreviation for millimeter and centimeter are respectively written as mm and cm with no period between or after either of the two letters. The abbreviation is exactly the same for both the singular and the plural terms. The square millimeter and centimeter are preferably written as mm^2 and cm^2 for measuring areas. The approximate equivalents for volumes are mm^3 and $cm.^3$ For units of mass each term for either the singular or the plural is abbreviated as follows: kilogram (kg) gram (gm) milligram (mg) and microgram (μg) with micromicrogram ($\mu\mu$g).

When measuring concentration the widest variety of terms has been permitted, although standard usage is concisely clear. One mole per liter is described as M/L with a millimole per liter as mM/L. One equivalent per liter should be abbreviated as q/L, and a milliequivalent per liter as mq/L; for one gram per liter gm/L and one milligram per liter the terms gm/L and mg/L are self-explanatory.

We are so accustomed to writing "the red cell count was 5,000,000" that we may perhaps hesitate at the scientific "$5.0 \times 10^6/mm^3$" for an erythrocyte count and "$5.50 \times 10^3/mm^3$" for a leukocyte count; usage has so sanctified the colloquialism. On the other hand, there is little or no excuse for what Ham* describes as that most confusing of terms "mg%." Its exact and only significance must be taken as milligrams of something in each

*Ham, T. H.: Laboratory data in clinical medicine. New England J. Med., 241:488, (Sept. 28) 1949.

hundred milligrams. The true abbreviation is therefore mg/100 ml or, when it applies, mg/L.

The author who uses the standard nomenclature will not only make his meaning more clear but will avoid the possibility of error due to the changes which must necessarily be made by those who must see his typescript through the steps of forming it into an acceptable printed page. He will also have the satisfaction of feeling that his readers will all know exactly what he is talking about.

CHRONIC ULCERATIVE COLITIS—AN ALLERGIC DISEASE

(Continued from Page 751)

REFERENCES

1. Alvarez, W. C.: Are antispasmodics of much value? Gastroenterology, 12:155, 1949.
2. Andresen, A. F. R.: The treatment of ulcerative colitis. M. Times, New York, 41:299, 1933. *Also:* Ulcerative colitis—an allergic phenomenon. Am. J. Digest. Dis., 9:91, 1942.
3. Auer, J.: Proc. Soc. Exper. Biol. & Med., 17:93, 1919.
4. Bargen, J. A.: Treatment of ulcerative colitis with salicylazosulfapyridine (Salazopyrin). M. Clin. North America, 33:935, 1949.
5. Bargen, J. A.: The Modern Management of Colitis. p. 163. Springfield: C. C Thomas, 1943.
6. Gray, I., Harben, M., and Walzer, M.: The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. J. Allergy, 9:394, 1938.
7. Gray, I., and Walzer, M.: The allergic reaction in the passively sensitized rectal mucous membrane. Am. J. Digest. Dis., 4:707, 1938.
8. Machella, T. E.: Significance of hyperalimentation in treatment of chronic idiopathic ulcerative colitis. Am. J. Med., 7:191, 1949.
9. Mackie, T. T.: The medical management of chronic ulcerative colitis. J.A.M.A., 111:2071, 1938.
10. Marks, J. A., Wright, L. T., and Strax, S.: Treatment of chronic non-specific ulcerative colitis with aureomycin. Am. J. Med., 7:180, 1949.
11. Rowe, A. H.: Gastrointestinal food allergy. J.A.M.A., 97:1440, 1931; Journal-Lancet, 56:120, 1936. *Also:* Clinical Allergy, Philadelphia: Lea & Febiger, 1937.
12. Rowe, A. H.: Seasonal and geographic influences on food allergy. J. Allergy, 13:55, 1941.
13. Rowe, A. H.: Chronic ulcerative colitis—allergy in its etiology. Ann. Int. Med., 17:83, 1942.
14. Rowe, A. H.: Elimination Diets and the Patient's Allergies. 2nd ed. Philadelphia: Lea and Febiger, 1944.
15. Rowe, A. H.: Delayed healing of abdominal wounds. West. J. Surg., 54:313-316, (Aug.) 1946.
16. Rowe, A. H.: Dermatitis of the hands due to atopic allergy to pollen. Arch. Dermat. & Syph., 53:437-453, 1946.
17. Rowe, A. H.: Discussion of chronic ulcerative colitis. J.A.M.A., 134:346, 1947.
18. Rowe, A. H.: Chronic ulcerative colitis, its allergic aspects, and treatment. Fall Graduate Course in Allergy, American College of Allergists, Nov. 9-12, 1948.
19. Rowe, A. H.: Fever due to food allergy. Ann. Allergy, 6:252, 1948.
20. Rowe, A. H.: Symposium on chronic ulcerative colitis. California Med., (Jan.) 1949.
21. Svartz, N.: Salazopyrine, a new sulfonamide preparation: therapeutic results in rheumatic polyarthritis. Acta med. Scandinav., 110:577, 1942.
22. Wohl, M. G.: Dietotherapy. p. 710. Philadelphia: W. B. Saunders & Co., 1945.

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Progress in Allergy

MISCELLANEOUS ALLERGY—1949

Critical Review of the Literature

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In past years, the subject matter of this miscellaneous review has been divided into separate components and the discussion has followed this same trend. Of necessity, some mention has been made of important and interesting papers which have been cited and reviewed by other reviewers for ANNALS OF ALLERGY. In the following few pages an effort has been made to avoid such duplication and to offer only those words which rightly belong in this miscellaneous category and which, because of the subject, probably would be omitted from the other specified groupings. An apology is therefore extended to the authors whose works otherwise might have been included and to the reader who might herein expect to find material more closely identified with some other particular phase of allergic management.

That the practice of allergy is not all song and dance has been aptly proven by the report of Blanton and Sutphin.[9] The honesty of the authors is to be commended. All of us in the practice of this specialty depend to a great extent upon the reaction of tests being recorded as positive or negative. Yet these authors have demonstrated that negative skin tests cannot be overlooked even though their report is one of a fatality. Their patient was a fifty-seven-year-old asthmatic woman who had been previously examined and tested with positive reactions to various inhalants and pollen. Control of the asthmatic symptoms had been accomplished with oral medication. Preliminary scratch tests had failed to give positive reactions on this occasion, so intracutaneous testing was begun. The site of the testing was the back. Marked, generalized complaints of allergic shock were experienced by the patient after fifty-six tests had been injected. Death occurred within a very short time, and at the interval, all tests were thought to have been negative, although no real effort had been made to record the degree of reaction accurately. Autopsy findings showed both lungs to be markedly voluminous and in a state of constant inflation. Subpleural hemorrhages were found in association with submucous hemorrhages in the trachea and bronchii. Obstruction and occlusion of the bronchial tree were in evidence with edema of the mucous membrane which had infolded as a result of the intense spasm. Such unfortunate happenings are extremely unpleasant to experience, and each allergist should abide by the rule that conservatism in all respects is a valuable adjunct to each procedure. The danger of skin testing is further emphasized by the report of Rosen.[103] Symptoms of generalized reaction and collapse were noted in a female patient a few minutes after the introduction of 0.05 c.c. of a stock solution of streptomycin in intradermal manner. She had had a rash on the dorsum of her hands and on her fingers for several months. Though she had had no previous therapy with penicillin or streptomycin, she had been exposed to contact with each drug. Recovery from the reaction was obtained with emergency measures, and eventual passive transfer studies revealed only a moderate reaction to streptomycin. These unexplained violent responses are particularly upsetting, to say the least, to the physician in charge.

A fatality following the use of a protein digest (Amigen) has been the subject

of a report by Coppinger and Goldner.[23] The hypersensitivity reaction occurred immediately after the administration of not more than 4 c.c. of Amigen, with death following in a period of sixty minutes with all the classical signs of anaphylaxis present. Subsequent to abdominal surgery for a bleeding ulcer, this forty-four-year-old man was given Amigen solution, 5 per cent in 5 per cent glucose. Immediately the patient became apprehensive and complained of respiratory difficulty. The infusion was stopped with only 4 c.c. having entered the vein. The signs of reaction were progressive, with death occurring with the onset of pulmonary edema. Passive transfer tests were done with the patient's serum with the blood having been removed from the auricle at autopsy. These tests were positive. The authors suggest that all patients should be previously tested before the administration of protein digests parenterally. Equally unfortunate in its overall coverage is the editorial[31] concerning the present status of graduate education in allergy. A recent survey has shown that in the United States there are only seventeen institutions which offer adequate training in the specialty of allergy. Of these seventeen, only twelve of them are council approved. It is the suggestion of the committee that all institutions group their medical subspecialties for postgraduate training. The fact was also lamented that the better types of residents and postgraduate students were not being sufficiently exposed to the allergic diseases and their control, with the result that few of the so-called top personnel were entering the study of allergy as a method of practice.

Present-day aspects of allergy is the subject of an interesting discussion by Salmon.[101] He reviews the highlights in the development of present knowledge of allergy. Mention is made of the anaphylactic studies of Sewall in 1882 with various incidences involved in the progress of this specialty to the present standards. Though the care of the allergic patient will demand the efforts of the specialist in many instances, the man in general practice has the opportunity to relieve much suffering and to make the diagnosis in many instances. Bullen[15] emphasizes the importance of the history in making an allergic diagnosis. He presents a very sensible approach to the various methods of skin testing and offers an answer to his title question, namely, what should the general practitioner do about allergy? The author feels that the nonspecialist may undertake the necessary diagnostic studies and carry out the indicated therapy. This answer may be fraught with a pitfall or two. The general practitioner may also refer the patient for study and complete the treatment in his own office, which to this reviewer would seem to be the most sensible if the referring physician does not care to refer the problem in its entirety for investigation and treatment. Simon[113] has a very good discussion of the basic principles of the allergy investigation. He presents a paper concerning the specificity of the allergic reaction and mentions the usual management of the various allergic diseases—in addition, a few paragraphs suggesting an allergic basis for acute rheumatic fever, chronic arthritis and a few of the other presently unexplained conditions. Though skin testing is an important part of the allergy investigation, the history, examination and laboratory tests are necessary components of the complete program. Such is the advice of Spain[115] who feels that environmental correction for the allergic patient is a necessity. He has informed the ear, nose and throat practitioner in the details of recording an accurate and important history. Because these physicians will see the reactions, Spain also has discussed for them the signs, symptoms and therapy of drug reactions with advice concerning the serum sickness type of reaction. The concept that the "asthmatic state" is a constitutional factor is adequately supported by Rackemann in his annual review.[96] Such an attitude explains to a great degree the tendency in predisposed persons to develop one or more allergic diseases. McGee[76] feels that these allergic tendencies and trends may be recognized in the first year of life. Such recognition should lead the physician to careful addition of foods to the diet, with each food being

added singly, and no further additions until a three- to five-day waiting period for possible reaction has been accomplished. He finds it rarely necessary to skin test infants under the age of one year. In general, better results in therapy can be expected in children than in adults, and this is no doubt due to the better co-operation obtained from the adults as parents than as patients. With the thought that the pathologic condition in allergy is reversible, McGee is encouraged by his management of pediatric allergy problems. Ratner[109] has written that allergy may develop in children whether they are born into allergic families or to non-allergic families All individuals are potentially capable of developing sensitivities. Fetal sensitization is possible in view of the ability of antigens or antibodies to be transmitted through the placenta. He recognizes the acquisition of hypersensitivity to be dependent upon constitutional or other factors peculiar to the individual. In addition, the amount of the antigen to which the patient is exposed is of importance. In Ratner's opinion, the quantitative factors are of greater concern than are the qualitative ones. Dietary regulation, environmental management, control of drug and serum therapy and reduction of recurrent pathogenic infections are important preventive measures to be accomplished. Skin testing in any age of patient is hardly worthwhile in drug allergy. Sherman[112] is of the opinion, and has the agreement of this reviewer, that an accurate history is diagnostic of drug sensitivity. Patch testing is occasionally of value, but the scratch and intracutaneous methods of testing are without value in an attempted diagnostic measure.

The usual estimate on the number of allergic patients in the general population has been recorded as 10 per cent. This figure can be accepted for most purposes, and is representative of the extent of clinical allergy. Prickman[93] states that the remaining 90 per cent may be sensitized under certain circumstances. This is particularly true with the administration of antitoxins, serums, penicillin or sulfonamides. Such reactions may be delayed or immediate in character. There is no sharp dividing line between the allergic and the nonallergic individuals. Prickman feels that the allergic reaction is a matter of threshhold, with this factor being lowest in the clinically allergic person. True allergic reactions are consistent and must meet the established criteria: symptoms must result from natural contact with a substance not provoking symptoms in the majority of individuals; the symptoms must disappear when such contact is avoided or prevented; and the original reaction must be reproduceable at will. He considers the allergic reaction to be a defensive process, with the symptoms being a resultant expression of contact with a noxious substance. "Failure to arrest allergic disease can be due to deficiencies in our understanding of the condition or to sins of omission or commission on the part of the physician who treats the patient." With such words, Cohen and Abram[19] present case histories illustrative of the reasons for lack of relief and improvement in the common allergic diseases. In their classification, mistaken or incomplete diagnosis is of the most importance and interest. Some patients considered as allergic are not truly in this status. Hence no improvement on allergic management can be expected, but often is anticipated. The symptoms may be initiated by allergy but continued by some other organic or emotional factor, the importance of which leads to continuation of symptoms in spite of supposedly adequate therapy. The failure to find the specific cause of the allergic symptoms is too frequently encountered. Inadequate therapy is one of the most important of Cohen's failure-clauses. If adequate co-operation of the patient cannot be obtained, then failure to improve will be the result. A word of caution should be extended to many physicians in this regard—the patient cannot be blamed for all failures of therapy! In many instances, the lack of proper explanation to the patient on the part of the attending allergist will result in the inability of the patient to adequately avoid the cause of the symptoms, even though such cause has been found, recognized and proven. Too much dependency on skin test findings alone will result in the failure

of the patient to show improvement. Similarly, the failure to appreciate the patient as an entity and to plan his management accordingly will meet with unpleasant therapeutic outcome.

The allergy factor in disease has been discussed by Cooke.[22] All manifestations resulting from antigen-sensitized cell reactions are included as allergic diseases. "Immediate" type of allergic response is shown by the reactions to air-borne allergens, as pollen, danders and dust. "Delayed" type of allergic response is shown by the tuberculin flare and is inflammatory in character. The antibodies, usually found in the globulins, are stimulated by contact of free cells with antigens. These antibodies may be beneficial, as in antitoxin, or their presence may be a liability as evidenced by allergic symptoms. Cooke states that there is still need for further study to prove or to disprove that sensitizing (allergic) and protective (immune) antibodies are the same. Histamine theory has failed to explain the delayed type of allergic response. He also has discussed the prevalence of allergy as a basis for the study of the pathogenesis of diseases of unknown cause—rheumatic fever, rheumatic arthritis, periarteritis nodosa, scleroderma, sarcoid, multiple sclerosis and the entire group of erythemas and purpuras. Cooke is a recognized advocate of his theory of the "earlier the removal of foci, the more satisfactory the results will be." Lesions affecting connective tissue have caught the attention of several authors. Duff[30] describes in detail the characteristics of connective tissue and the pathologic sequences seen in the various diseases—those mentioned above as of unknown origin. He postulates that a variety of factors, including hypersensitivy, may lead to the release of enzymes in connective tissue followed by destruction of collagenous and elastic fibers and to changes in the intracellular ground substances. A common etiology cannot be implied by similar morphological lesions. Criep[25] feels that hypersensitivity and collagen disease are often somewhat related. Serum sickness, which is a manifestation of allergy, is often characterized by collagen disturbance. More weight is added to this concept with the induction of periarteritis nodosa in both man and animals following the administration of sulfonamides or foreign sera. The clinical manifestations of rheumatic fever can be reproduced experimentally by sensitization. He adds a word of warning that it should not be assumed that the presence of collagen changes in man are necessarily and always caused by hypersensitivity. He echoes the views of the above authors that a common pathology does not necessarily bespeak a common etiology. In this same regard, Estrada de la Riva[35] advances a theory considering the disease, tropical eosinophilia, as an allergic reaction rather than as a nosological entity. He has shown that the allergic reaction is one of the organism to embryonic elements, extrinsic or intrinsic, with the hematopoietic system as shock tissue.

Occasionally periarteritis nodosa may be prolonged and not fatal. This is the standard of King[62] in his description of his patient with recognized and histologically proven lesions. A nonfatality over a period of more than two years is an oddity, to say the least. This patient, however, had asthma and arthritis of four years' duration with hospitalization necessary on several occasions. Eosinophilia varied from 8 to 54 per cent on several examinations, but at no time was there any evidence of renal involvement nor hypertension. Though the cosinophilia continued and she developed painful skin nodules from time to time, the course of the disease was followed over a period of many years. Gelfand and Aronoff[38] found that in their fourteen reported cases, 57 per cent had associated bronchial asthma. There was a noticeable rise in the incidence of periarteritis nodosa after the introduction of sulfonamides. In review of hospital records, they have recorded that there were relatively few cases in the years preceding the use of chemotherapy. In their fourteen cases, cosinophilia over 10 per cent was noted in 43 per cent of patients. The usual textbook picture of periartertis nodosa lays stress on the cardiac, renal and pulmonary aspects of the disease. Ralston and Kvole[97] could

find only one instance wherein hypertension was mentioned by the author. The kidney has been found to be involved most frequently with the vascular inflammatory lesions being the most characteristic pathological change. These authors have studied thirty cases with respect to the clinical evidence of renal damage; twenty-five of twenty-eight showed very early abnormal urinary findings, with the most common change being an early albuminuria; twenty of twenty-nine showed hypertension. The above prolonged instance of periarteritis nodosa gains in clinical rarity when it is reported that the average duration of illness in these thirty patients was found to be twelve months, with twenty of the thirty patients expiring within two to eight months after the onset of the symptoms. Again, it is emphasized that the site of the involvement is of utmost importance. It is concluded by Ralston and Kvole that there is no consistent correlation between the clinical evidence of renal damage and the specific pathological types. Well-distributed abdominal pain was the most frequent symptom noted in a study of thirty cases by Wold and Baggenstoss.[130] Five cases showed no lesions in the abdominal viscera although the complaint of abdominal pain was the most prominent symptom. Sweeney and Baggenstoss[120] found eight cases of lung involvement with arteriolar and parenchymal lesions. Fifty-two per cent of the cases studied had complaints of peripheral neuritis, as reported by Parker and Kernohan.[88] Eight cases had mononeuritis multiplex, but in seven instances the pattern was symmetrical multiple neuritis which clinically did not differ from infectious polyneuritis.

Harris and Laws[53] offer clinical and experimental proof that periarteritis nodosa has an allergic reaction as its base. If this disease is to be classified as an allergic disease, then several criteria must be met: perivascular infiltration with a fair percentage of eosinophiles and polymorphonuclear cells, edema of the vascular walls, fibrinoid necrosis and the variable factor of eosinophilia. The acute stage of the disease is manifested by an acute inflammatory infiltration reaching any of the three layers. Involvement of only one side of the vessel—segmental involvement—is characteristic of periarteritis nodosa. They feel that with better diagnostic work, the rate of recovery will increase. This reviewer again calls attention to the above remarks regarding the location of the lesions as an index to the rate of recovery or fatality. Gratifying clinical results in the therapy of rheumatoid arthritis have been reported by Rockwell.[102] In a series of fifteen adults, only two patients have failed to show improvement with the intravenous use of histamine, according to the principles of Prince, which produces a generalized flushing on administration. Some of the cases were given prolonged acting histamine in the form of ethyl histamine carbonate. Pain usually disappeared with therapy, and swelling was usually absent in three to six weeks. Blood sedimentation rates returned to normal within three to six months. He feels that the predominating pathological finding in rheumatoid arthritis is an impairment of the capillary circulation by a constricted capillary bed. In addition to the histamine therapy, bacterial sensitization and the removal of offending foods were adjunctives. Though he considers it unwise to attribute the entire syndrome of rheumatoid arthritis to food allergy, Zeller[132] presents four interesting problems in which dietary management was beneficial. Skin tests, both scratch and intradermal, were of relatively little value. The most effective and direct diagnostic aids were the food ingestion tests and the white blood cell response determinations. Concomitant allergic findings, a positive family history of allergy, positive skin test and passive transfer tests, blood eosinophilia, and x-ray studies are a few of the reasons for classifying some cases of arthritis as having an underlying allergic hypothesis. This is the opinion of Miller[81] in his presentation of three cases of allergic arthroses. A table is presented in offering a differentiation between allergic and nonallergic arthritis.

The subject of gout has been presented from the allergic standpoint by Hark-

avy.[51] He feels that heredity is an important factor in the production of the disease. Differentiation from other forms of arthritis can be served by the frequency of hyperuremia. He feels that the patient with gout may have an hereditary defect in his purine metabolism. There have been no previous reports of pollen or the synergistic effect of pollen and foods having any effect upon the initiation of the symptoms of gout. Harkavy reports three cases in detail in which it was possible to precipitate gout by allergic excitation. The ingestion of purine-and-fat containing foods was met without incident unless sensitizing substances were present. In one reported case, the symptoms were coincidental with the onset of the pollen season, and subsequently symptoms could be reproduced with pollen injections. This was true if wheat, one of the offending foods, were in the diet or if the pollen were in the air. Bacterial sensitization in two of the three cases suggests that the swelling in these instances was due to a vascual tissue reaction mediated by similar allergic mechanisms.

That desensitization is superfluous in insulin allergy is the contention of Hult and Jorpes.[58] They state that thoroughly purified insulin is tolerated by all diabetics. Even though some symptoms of sensitivity may be expressed, such conditions are lost after a continuation of the insulin for several weeks. Any difficulty can be obviated by using recrystallized insulin. They do feel that it is conceivable that a few extremely hypersensitive patients may become sensitive to the insulin protein. A "new concept in the treatment of allergy" presents a bit of discussion upon Ethylene Disulfonate. Ketcham[61] demonstrates that there are three paths for the chronic asthmatic or allergic patient to follow once he has been treated with this drug. These paths lead to good improvement, exacerbation of symptoms or no relief. The preparation of the patient, with avoidance of tobacco, alcohol, opiates, barbiturates and a few other materials is stated to be important. The reason for such avoidance seems to be that these products "have a tendency to inhibit dehydrogenase and the oxygen carrier system." The majority of reports concerning the use of this drug continue, as in the past, to state that Ethylene Disulfonate is without value in the treatment of the allergic patient. Phillips[90] found that 118 women between the ages of twelve and sixty years reacted negatively to a 1:5 dilution of Synapoidin. Twenty-five had positive reaction, with one patient showing shock symptoms from an intramuscular injection. The active allergen resides in the anterior pituitary hormone or its combination with chorionic gonadotropin. Antuitrin-S was used as a control test. Maximum dosage was 0.3 c.c. given intradermally twice monthly; thirty-five of forty-nine patients were completely relieved. Any dosage did not exceed the point of relief.

Thomas and his co-workers[123] have found that urticaria was the chief reaction to penicillin therapy in about 10,000 cases of syphilis. It occurred in about 2.5 per cent of the patients treated. The reactions were delayed in type, for the most part. This did not prevent the continuation or the resumption of therapy in the majority of treated patients. Another reaction, less frequently encountered, was an exacerbation of the secondary lesions of syphilis. This usually was noted at about the sixth to the tenth day following the institution of treatment. Lesions similar to an acute fungus infection, but with no demonstrable fungus found, were also noted as part of the penicillin reaction. Though the urticaria seemed to be recurrent over a period of several months, there was no noticeable permanent penicillin sensitivity demonstrated or reported. Treatment of pernicious anemia has brought to light specific instances of liver extract sensitivity. Malmros and Herner[80] desensitized two patients who had developed neurological lesions, and treatment with injectable liver extract could be continued. Fifteen other patients were adequately treated with folic acid and a stomach-liver preparation. It is recognized in general medicine that the use of folic acid is not to be accepted as adequate therapy in place of liver extract because of the failure of the former sub-

stance to affect neither the neurological lesions nor the progress of these symptoms.

During the past two years, this reviewer has had the opportunity of treating three cases of cold hypersensitivity. This may not seem unusual until it is learned that all three patients originated in the same part of the state and had their residences within three miles of each other in the country. They were not acquainted nor related. One of these three had symptoms to the degree of shock and collapse on an occasion when he was in the process of draining a small pond on his farm. Though his history of periodic swelling and urticaria upon exposure to cold had extended back into childhood several years preceding this severe attack, no accurate nor causative diagnosis had been made. Mullinger and Bogoch[85] report a severe case of cold hypersensitivity in a young woman who developed syncope while swimming in cold water. She was well controlled with Benadryl orally, in contrast to the personal experience in the three cases cited above. The benefit from this drug, however, was only transient, as the effect was dissipated within thirty-six hours. Histamine and cold desensitization were met with failure, which is in agreement with the reviewer's experience. These three patients have been comfortable while spending the cold Iowa winters in the South or Southwest. In this climatic regard, Schutzbank[108] has reported that 72 per cent of the patients coming to Arizona because of allergic disorders were the recipients of relief. Of 100 asthmatic patients, seventy-four received from 50 to 100 per cent relief. As a rule, the patient with an intrinsic bronchial asthma and a chronic sinusitis did not fare as markedly. In selected cases, the author felt that a change of climate should be recommended but that this advice should not be given to any and all allergic patients. The psychic aspect of the change may be more important than the climatic consideration. Arizona is dry and it has been stated that the dust-sensitive patient does not do as well there as in other regions. Stevenson[110] recommends the southern third of Arizona for the patient desiring abundant sunshine, warmth and little rainfall. Seasonal changes in that locality are seldom a noticeable source of distress to any patient. In contrast to the above climatic report, this author reveals that all forms of sinusitis, bronchitis and bronchial asthma are the receivers of health and happiness. He does state, however, that the infections type (intrinsic?) of bronchial asthma will be relieved only after a period of several months or years in the Arizona atmosphere.

It has been often remarked, though far from accurately recorded, that only the so-called higher type of patient will find time to have allergic complaints. McAllister and Hecker[75] have reviewed a control group of 757 personnel and a test group of 1,875 psychiatric patients. Among the controls the survey was made during a ragweed season, and 21 per cent revealed major allergies, with 13 per cent having physical signs at the time of survey. The majority of the test group were definitely psychotic, with the incidence of allergy by history being 5.7 per cent, with physical signs of such hypersensitivity being demonstrable in 2.9 per cent. They wisely conclude, therefore, that the incidence of allergy is definitely less in the psychotic group.

Unrecognized allergic symptoms are often the causes for tonsil and adenoid removal. This has been brought forth by an article well written by Clein.[18] Following surgery, the mother usually returned with the child still having a good degree of nasal congestion and stuffiness—the original reason for the operation! All too often the diagnosis of allergic rhinitis is made postoperatively. In 27 per cent of Clein's reported instances, the patients who complained of lymphoid tissue regrowth were actually undiagnosed, untreated allergic children. A regrowth of lymphoid tissue was present in only 3 per cent of the investigated, treated group of children. It cannot be emphasized too strongly—and certainly anyone sufficiently interested in allergy to read this review does not need the advice—that the removal of the tonsils and adenoids does not relieve the symptoms of aller-

gic disease. The asthmatic patient presents the greatest problem as far as anesthesia is concerned because of the difficulty in breathing, increased pulmonary secretions, edema and congestion. Brenneman[13] feels that each of these patients should be well oxygenated. Ether abolished vagal reflexes and relaxes the bronchial musculature because of its sympathomimetic action. Rate and depth of respiration are increased with ether anesthesia by virtue of its stimulating effect on the respiratory mucosa. He feels that ether for these reasons, is the most useful agent. Nitrous oxide, ethylene, cyclopropane and others seem to be satisfactory, but Pentothal Sodium, because of its parasympathomimetic action, has a tendency to cause bronchial constriction. Seldom is there a reported instance of hypersensitivity to any of the inhalant anesthetic agents, although cyclopropane sensitivity is not uncommon. A great deal of the success of anesthesia in the allergic patient depends upon proper preparation of the patient, selection of the correct medication preoperatively and the choice of the anesthetic agent and technique. Substantiation of Coca's nonreaginic allergy is given impetus by Meyer.[83] He presents evidence to show that the pulse dietary method of diagnosis is a distinct weapon in the hands of the allergist. He feels, however, that it is too time-consuming for routine usage and has substituted intravenous histamine as the answer.

During the past two years, the attention of most allergists has been drawn to the public hearings held in Washington, D. C., in November, 1947, and January, 1948. These hearings were in regard to the possibility of allergy to cottonseed oil and the edible derivatives of this and other oil seeds. The testimony of the expert witnesses —G. T. Brown, R. S. McGrath, H. S. Bernton, J. H. Mitchell, K. D. Figley, M. H. Loveless—has been compiled in book form and published by the National Cottonseed Products Association, Inc. of Memphis, Tennessee.[122] If obtainable, the pleasant reading of the valuable material contained therein is an evening well worth the time of any allergist. Most of us have been in the habit of informing our cottonseed sensitive patients that they must, for fear of alarming reactions, avoid all products containing "vegetable oil." The average manufacturer does not differentiate between the edible oils and has found it convenient and practical to label any oil-containing product simply as such. This testimony should put an end to what Bowen[10] has described as an allergic ritual. Figley, one of the above testifying expert witnesses, has reviewed the material and presented it for general consumption. He has verified the fact (quoted by Bowen) that there is not a single reported authentic case of cottonseed oil sensitivity. In the one or two instances where such confirmation was in doubt, the suspected oil-sensitive patient was found to be nonreactive when the material was given and tested under controlled conditions and in masked form. It is accepted that the amount of protein in cottonseed oil is a negligible fraction. Figley has reviewed the above testimony in his presidential address.[36] Allergenic sensitivity to the water-soluble protein fractions of the various oil-producing seeds is common and severe. This should not be taken as an indication of oil sensitivity, however. The causative factor of any oil sensitivity must be some substance other than the water-soluble proteins of the producing seed. Additional evidence in published form is shown in the article by Bernton, Coulson and Stevens.[3] They describe two patients who were sensitive to the water-soluble protein of cottonseed. One of these (a physician) maintained that any contact with cotton would produce allergic symptoms and that the ingestion of cottonseed oil was followed by gastrointestinal symptoms. Masked feedings of several unlabeled (except for identification number) oils did not furnish adequate evidence of cottonseed oil sensitivity, in that the patient could not distinguish which oil was incriminated in his history. The authors feel that such controlled experiments fail to reveal any association between the water-soluble protein sensitivity and the clinical sensitivity to edible cottonseed oil.

In this same regard, there has been much discussion and debate concerning the sensitivity a patient may have for the parent source of other oils as contrasted to the specific oil sensitivity. Wolf[131] has inquired regarding the suspected sensitivity possessed by his patient for sesame oil. This was experienced and suspected upon injection rather than ingestion. Stenbuck[117] feels that his patient is responsive in an allergic manner (migraine) to the ingestion of corn and corn starch, but that no reaction could be elicited upon the use of corn syrup. Cazort[16] has carefully tested a suspected case of oil sensitivity, but more will be stated concerning this problem in a later paragraph. Detwiler[29] has disagreed with the established principles of Randolph and Rinkel in their method of determining food allergy. Though he feels that skin testing for foods is most unreliable, this author is of the opinion that an elimination routine is the one of choice. He places his patients upon an exclusively milk routine and adds foods as they seem to be indicated.

On August 3 and 4, 1949, there was another public hearing before the Federal Security Administrator. Though this was termed the "Bread Hearing," the decisive testimony concerned the likelihood of a patient being sensitive to corn and to the corn products or derivatives. Randolph testified that recognized sensitivity had been determined for corn starch as well as for the whole corn product. He was in favor of proper labeling of all food products in which any of the corn derivatives were contained.[98] Brunton,[4] in his testimony, felt that he did not see the 25 per cent corn-sensitive patients as had previously been described by Randolph. He was of the opinion that corn starch, corn syrup and dextrose did not act as allergens. He presented answers to a questionnaire that would tend to show that such a large percentage of corn-sensitive patients was not usually seen in the average allergy practice. Cazort[17] testified concerning his patient who was known to be sensitive to whole corn. Under controlled conditions, this patient had been given one ounce of corn syrup in Coca-Cola and no symptoms could be elicited. Later, one-half ounce of corn oil was given without producing symptoms. The same patient held a half a teaspoonful of raw corn starch inside his lip with no immediate nor delayed reaction. Cazort felt that this confirmed his opinion that the antigen of corn oil, corn starch or corn syrup was "negligible clinically." This patient had a marked, immediate, wheal-type reaction on scratch test with corn meal. A repetition of the test with contact to the lip with corn meal was followed by immediate tingling of the patient's tongue, and with redness and swelling in the area of the tonsillar pillars. Similar feeding tests with corn meal in this patient had been associated with almost alarming symptoms upon ingestion. Halpin[46] added to the testimony with a description of a patient clinically sensitive to whole corn. This patient had had immediate asthma, urticaria and almost collapse upon the ingestion of corn on more than one occasion. Allergy investigation had revealed, in part, a marked immediate wheal-type reaction to corn extract and corn meal on scratch test. Masked feedings of products unknown to either the patient or the physician were not associated with any symptoms, either objective or subjective. It was later determined, just prior to the presentation of the testimony, that the feedings had been, in order, a control of arrowroot, tapioca and corn starch pudding. The sweetening agent was determined to have been sucrose. The puddings all had similar appearance, consistency and taste. The conclusion was therefore drawn that this known corn-sensitive patient was not reactive to corn starch and therefore the antigen in corn starch was negligible clinically. Rawlings[100] had performed controlled feeding tests in the same manner with the same results. He described the patients and the ingestion of masked puddings. He felt that his patient was allergic to fresh corn but not sensitive clinically to corn products nor derivatives.

Of twelve patients who received a full course of intramuscular penicillin therapy, seven were apparently benefited. The complaints were those of chronic asthma. It was necessary to discontinue treatment in three patients because of reactions.

Sterling, Fishman and Sharpes[118] feel that the improvement is due to the specific antibiotic effect of the drug, which thus reduced the frequency of bacterial infectious processes and exposures. In the past few years, much writing has been relative to the use of radon or radium to the nasopharynx of asthmatic children. In answer to a query offered by Pinesss[81] it was the feeling of Barnet[2] that such procedure was well worth while. Hansel[47] stated that the use of radium applicator would be entirely nonspecific in nasal allergy. Its use should be advised only in those instances where all other forms of accepted therapy had been judged a complete failure after adequate trial. Jones[62] had no unpleasant experiences with radon and radium in the treatment of lymphoid hypertrophy of the nasopharynx. He describes the currently accepted method of treatment as using 50 mg. radium filtered with 0.1 mm. monel metal. The applicator is applied in each side of the nasopharynx so that the radium is close to the orifice of the eustachian canal. The applicator is left *in situ* for twelve minutes on each side. Treatments are repeated at stated times and intervals depending upon the result. The patients of Cohen and Fisher[20] were divided into groups depending upon the amount of adenoid tissue, the degree of hyperplastic sinusitis, and an elevated sedimentation rate. They did not consider this form of therapy as a panacea for all forms of asthma in children. They did find it to be a good auxillary, however. Expected improvement was noted about seventeen weeks after the application of a radium applicator for six and one-half minutes in a dosage of 100 mg. The higher the sedimentation rate, the better seemed to be the result. More relief was obtained in the group possessing a small amount of adenoid tissue as compared to those with a great deal of the tissue present. Patients with normal sinuses seemed to fare better than those with hyperplastic sinusitis.

The importance of allergy in the average ear, nose and throat practice has been emphasized by Hansel.[48] He lists the frequency with which the nose and paranasal sinuses are involved, and in order they seem to be (1) allergy, (2) allergy with secondary infection, and (3) suppuration. A good discussion is presented of the symptomatology, bacterial flora and pathology. The examination of the cytological specimens is of great importance, and instructions are given, with which most allergists are, or should be, familiar. As part of the same symposium, Black[7] discusses the history and its importance. Determination of dosage, with indicated titration and low-dosage requirements are a part of this presentation. Ashley[1] adds that the success of allergy management depends upon an accurate diagnosis. He advocates extremely low dosages in therapy. Of all factors, he feels that the inhalants are of the utmost importance with the house dust substance being foremost. Although the allergen, house dust, is recognized as being of greatest importance, little has been determined quantitatively of the nature of the active constituent. An editorial[32] calls attention to work that has been done in this regard. The paragraphs quote from published works of Rimington, Stilwell and Maunsell who have described a purified antigen containing 25 per cent hexose and 2.5 per cent nitrogen. Before and after mild hydrolysis, the antigen shows two main components electrophoretically: one mobile and colored and the other immobile and colorless They are somewhat similar in composition and antigenicity. Harrell[52] continues the recognition studies of allergy by the otorhinolaryngologist. He emphasizes the importance of avoiding as much intranasal medication as possible. If used at all, this should be nonirritating, isotonic and with a slightly acid pH. Because they are mostly alkaline, sulfonamides should be limited in their use in the nose. Surgical procedures should be kept at a bare minimum, with submucous resection and antral windows deferred until an adequate allergy study has been made and followed. The soft tissue of the turbinate is the primary shock organ in allergy of the upper respiratory tract. This is the statement of Schenck.[107] The pathologic picture is a thickening and hyperplasia of the epithelium, edema of the basement

membrane and edema with eosinophilic infiltration of the stroma. A specific allergen is capable of precipitating all these as secondary phenomena to vascular changes. The efficiency to combat infection is definitely lowered in this type of allergic tissue. A radical ethmoid sinus attack is indicated only in failure of allergy program. Turnbull[126] presents twenty-five cases illustrative of various manifestations of allergy. There is a slight feeling that all of these patients are not truly allergic, as shown by his description of Case 16: a thirty-five-year-old man who consulted the author with no presenting complaints but did admit upon questioning to having had "mucus in his throat." This disappeared in two weeks with adequate dietary management.

The high incidence of allergy in bronchiectasis and chronic bronchitis emphasizes the importance of proper allergic therapy in some infections processes of the lungs. Davison[27] found that 76 per cent of the patients with bronchiectasis were allergic. All had undergone bronchoscopic examinations. Green[11] has reported on the use of aerosol penicillin in allergic patients with respiratory infections, with the coverage being for the year October, 1946, through October, 1947. Over 200 aerosol treatments were given to seventy-nine allergic patients. All symptoms were referrable to the respiratory tract. The average patient was given 10,000 units of penicillin by aerosol with epinephrine 1:1,000 or some other similar solution. The author feels that this has been an adjunct of use to his forty-two cases of asthma, eight cases of seasonal hay fever (why the penicillin?) and twenty-nine patients with allergic rhinitis. Maietta[79] has used epinephrine 1:1,000 as an aerosol with good results in bronchial asthma. Its action here is that of a topical vasoconstrictor. The relief of mucosal edema dislodges the inspissated mucus. Bronchodilation is a secondary effect of the medication used in this manner. Usually 0.5 to 1 c.c. is given with oxygen at a rate of 6 liters per minute. He has reported on this medication as used in seventy-three patients with excellent results. Markan[82] and his co-workers have reported on the use of intravenous oxygen in bronchial asthma. The rate of oxygen intravenously is 600 c.c. per hour using the Ziegler Technique and apparatus. It is permitted to flow from two to seventeen hours. Vital capacity was increased in all cases from 300 c.c. (30 per cent) to 1,300 c.c. (87 per cent). The increased vital capacity remained for as long as eight months in some cases, but there was a recurrence of symptoms in all instances within six months. Additional aids in the relief of bronchial asthma are found. Reiser and Ferris[101] have used the Drinker respiratory in three cases of bronchial asthma. Two of these died as a result of cerebral anoxia (??) because the procedure was delayed in action. The application of positive pressure to the chest wall and abdomen is thought to be a good adjunctive to the routine treatment of severe bronchial asthma.

Levin[72] calls attention to the importance of soil molds in respiratory allergy. She states that in Chicago the most important clinical mold is Alternaria. By the slide method, only Alternaria, Hormodendrum, Helminthosporium, rusts and smuts can be identified. Hormodendrum is the second most frequently found mold on the slide. Alternaria is seasonal as well as perennial and has an affinity for wheat and grains. In their office (Unger's) a mold mixture is used for therapy. This is made up of Alternaria 50 per cent, Hormodendrum 30 per cent and the others 20 per cent. Good results are obtained. Prince and his co-workers[94] have given the green light to their extract, labeled Alternaria No. 33. They have interesting tables to show the superiority of this extraction in Alternaria-sensitive patients and in control studies as well. This reviewer can second the statements, for this extract has been found most reliable in the examination of many Alternaria-sensitive patients, and in comparative studies with other commercial extracts. They have demonstrated that a precipitation with nine volumes of acetone gives an extract of higher potency than any other previously studied material. That air-borne molds may be either a primary or a contributing cause of respiratory allergy is the contention of

Eisenstadt.[34] The predominant molds in the Minneapolis area are essentially those as given above for the Chicago zone. Penicillium and Aspergillus are perennial contaminants with the rest being primarily seasonal. Multiple mold sensitivity has been found to be the rule, rather than the exception. Reactions were found to be clinically significant in 29 per cent of all the patients tested (380) and were of direct, first-hand importance in 11 per cent. Bieberdorf and Argabrite[5] feel that better mold extracts can be prepared by the use of protein-free media. This eliminated the additional number of washings, and yet such extracts were more potent though they contained the same nitrogen value as their predecessors grown on protein media.

Inhalant allergy as a cause of dermatitis has been propounded by Tuft.[124] The outstanding offenders in his report have been dust, ragweed and wool. The initial symptom of such inhalant dermatitis is intense itching. Once the lesions are present, other factors such as emotional influences and upsets may play a decided role in the aggravation of symptoms, signs and duration or extent of the appearance. Several illustrative cases are cited. In some geographical areas, an inhalant mold sensitivity is also of primary consideration. Though it is an important, neglected factor, inhalant allergy is not the sole cause of atopic dermatitis in older children and adults. The author emphasizes the point that proper local therapy by a *good dermatologist* is very important for good results. A case of hereditary angioedema has been reported by Sheldon, Schreiber and Lovell. These authors[110] present a case report from a family wherein edema affected three and possibly three additional members in two generations. Histamine and intravenous Benadryl may have been beneficial in some respects but they did not prove adequate in protecting the patient from fatality. Death was due to uncontrolled edema.

There has been considerable writing and literature concerning the use of undecylinic acid in the therapy of psoriasis. Perlman[89] administered the drug orally to seventeen patients with definite psoriasis and to eight patients with neurodermatitis. Excellent results were revealed. Gradually increasing dosages of the drug were given until a total of 7.5 grams were taken daily. All cases showed improvement with pruritic relief, and no harmful effects were noted even after prolonged therapy. Sheldon[111] used undecylinic acid without benefit in three patients with atopic dermatitis. The first patient received peak dosages of 6 grams three times daily for six weeks with no influence upon the severity, progression or duration of the lesions. The dermatitis was typically an atopic eczema of long standing. The second patient had a life-long history of eczema and his peak dosage was 4.8 grams three times daily. Therapy was continued for eight and one-half weeks. The same dosage was given to the third patient, a young lady with eczema. Treatment was continued for five weeks before failure was recognized and admitted. Ointments containing mercury often will lead to a prolongation of the lesions of plant dermatitis. Underwood and Gaul[128] decided upon this as a result of 152 exacerbations of dermatitis in 202 patients. These treatment reactions occurred most frequently at the site of the original lesions. Edema, vesiculation, bullae, hemorrhage and pustulation were the usual signs of such reaction from therapy. Leider and Baer conclude from their experiments that it is impossible to transfer passively allergic eczematous hypersensitivity.[69] Dermatitis was produced in six sensitive patients by patch testing for forty-eight hours. When the produced reactions had reached the stage of involution, cantharides blisters were raised on the healed sites. The injection of this blister fluid into the skin of normal persons failed to react in the expected manner when patch tests were applied to these prepared areas. Not all contact lesions are of the typical type. Urticarial lesions produced by contact were somewhat of a rarity. These were determined by Cole, Marmelzat, and Walker.[21] Their patient had suffered with giant urticaria of several weeks' duration. Efforts at the usual measures of relief were to no avail, until it was revealed that one flare-up during hospitalization

was associated with the use of an estrogenic cream. Past exacerbations were also connected with the use of this agent. Aminophylline has been used primarily in the therapy and relief of the allergic symptoms of bronchial asthma. Turner[127] treated thirty-five patients in the emergency clinic at Grady Hospital, Atlanta, Georgia, for urticaria with this drug by the intravenous route. One patient, in particular, showed dramatic improvement in the lesions and complaints that were thought to have been due to a spider bite. Complete relief was experienced by fifteen of the thirty-five patients and partial relief in eleven. The effect of the aminophylline was comparable to that of epinephrine.

Hanutz and Grimell[55] have carried out studies to determine the incidence and severity of reaction to the various forms of prolonged-action penicillin. One hundred and forty-two patients were used in this experiment; 100 of them had penicillin in beeswax and oil; sixty-three received procaine penicillin G in peanut oil, and seventeen had procaine penicillin G in aqueous suspension. Some patients were given more than one type of injection. Eleven patients developed sensitivity reactions among the 100 that had been given the beeswax and oil preparation. Only one reaction occurred in the procaine penicillin G in peanut oil group while no reactions were found in the aqueous suspension classification. They recommend the abandonment of the beeswax and oil preparation of the drugs, because this substance seemed to be the sensitizing agent. Samitz and Horvath,[105] on the other hand, have presented two patients in whom the reactions seemed to be due to the sensitivity to the penicillin itself. In such instances, testing the patient is accompanied by some danger of exacerbation and continuation of the lesions under therapy. Intracutaneous testing for drug sensitivity is unreliable in the opinion of Hansen-Pruss.[50] In the past two years, he has studied a group of twenty-six patients suspected of being sensitive to drugs. Their particular interest was in the group of medication of analgesic or antipyretic effects. Intracutaneous tests were done with solutions of the suspected drug, and to serum obtained from patients supposedly saturated with the drug. Contact tests were done on six patients and passive transfer studies were carried out on an additional five cases. Further work included testing "blister fluid" and actual readministration of the agent. Test and control patients responded in the same manner to the intracutaneous test, and hence this method proved unreliable. Passive transfer studies showed that aspirin is a strongly allergenic substance but they were not dependable for definite conclusions of specific sensitivity.

Until recently it has been a problem with this reviewer to adequately correct infantile eczema with substitution of a soybean preparation for milk in the diet of a milk-sensitive patient. The difficulty usually arose with a call from the mother seeking information as to methods to correct a moderate to severe diarrhea in the infant whose skin lesions were clearing with such substitution. Glaser[40] answered my questions with the addition of one or two teaspoons of Kaopectate to each bottle of soybean milk. He went further to offer a very adequate substitute for the infant who reacted to both milk and soybean mixture. Quoting from a previously published article[41] he listed the ingredients of a strained meat formula which is of sufficient importance to bear repetition in this review. Direct copy of this formula is shown on the opposite page.

The atopic and contact types of infantile eczema are based on allergy, but the conditions named numular eczema, seborrheic dermatitis and fungus infections—all of which are often classified as eczema—are not upon an atopic basis. Hill[56] does not believe that all positive cutaneous reactions are of clinical significance. To properly determine whether a food should be incriminated as a cause of the eczema, it must be eliminated from the diet, but care should and must be taken to insure an adequate, nutritious intake of food. Milk should not be removed from the diet unless a positive skin test reaction to milk has been elicited. Soybean substitution

is more successful than the use of goat's milk. Some forms of infantile eczema are due to contact sensitization rather than ingestion. Antihistaminics and unsaturated fatty acids have been generally disappointing in their relief of the lesions. Local therapy is incomplete without the additional aid of proper bandages for protection and prevention of further irritation of the lesions through scratching.

STRAINED MEAT FORMULA

Strained lamb (or other strained meat)	1⅛ cups
Oil—Sesame, olive or Mazola	2½ teaspoons
Sugar	2⅔ teaspoons
Starch—potato, tapioca, rice	2⅓ teaspoons
Calcium carbonate (get 4 oz.)	1 teaspoon
Ordinary table salt	½ teaspoon
Water	5 cups

Heat water in the top of a double boiler until the water in the outer boiler starts boiling. Add the sugar, salt and calcium carbonate. Mix the starch to a paste in ⅓ cup of cold water and stir into the water in the top of the double boiler. Cook the mixture for 45 minutes in the top of the double boiler, stirring occasionally to prevent lumping. If necessary, add water to allow for evaporation. Then add the strained meat and oil and mix thoroughly. Make up to 1 quart with boiled water. Bottle and use as formula.

Simon[114] has described fourteen cases in which human dander has been classified as a distinct cause of the eczema. He believes that this is the most important known allergenic excitant of the disease but states that it is likely that this is not the most important existing allergenic excitant. By testing, he has determined that the lesions of certain cases of atopic eczema contained an eczematogenous agent which was not a primary irritant but was most likely an allergen of undetermined chemical nature and biologic origin. Leider and Furman[70] describe causative factors of dermatitis ranging from occupational substances to "falsies" (non-occupational?).

So much has been written in the past few years concerning the antihistamine drugs that no attempt could possibly be made to review the literature in this space. The material is worthy of a separate review in itself. Besides, the journals are filled with comparative experiments lauding one and mentioning others to such a degree that a reviewer would be in a constant whirl trying to maintain some sort of equilibrium and balance. Ocular allergy has responded well to the use of Antistine eye drops. Hurwitz[70] has used the drug locally in fifty reported cases; 84 per cent of these patients were the recipients of benefit. Most relief was experienced by the ragweed sensitive patients. The drug seems to have a cumulative effect. Two of his patients were adequately relieved of their associated photophobia. The immediate effect of Antistine is contraction of the superficial vessels and a blanching of the conjunctiva. Vascular constriction is prolonged and not followed by secondary vasodilatation as is noted with epinephrine. There is also a slight anesthetic effect with Antistine. Loveless[74] has listed her preference for the antihistamine drugs in the order of: Pyribenzamine, Trimeton, Neo-Antergan, Decapryn, Thephorin and Antistine. These drugs were compared clinically and their efficiency was about in the order as listed. Of the above medications, Thephorin and Antistine were said to be associated with less side effects, while Decapryn seemed to disturb more patients than the other drugs. Her work was done with 113 patients suffering with ragweed hay fever. Harris[51] found essentially no difference nor preference in the five drugs studied in various allergic cases. Hydryllin semed to be more effective in bronchial asthma than did the other antihistaminic preparations used by him. Pyrrollazote was thought by Zolov[137] to be less effective than some of the other more commonly used medications of this group of drugs. That the use of antihistaminic medication in allergic conditions is not always beneficial is stated in a

few paragraphs by Braden.[12] He has described the occurrence of urticaria due to the use of Benadryl and Pyribenzamine. Aggravation and actual production of urticarial lesions were witnessed in his patient under treatment for ragweed seasonal hay fever. Schilling[109] had a similar experience with the use of elixir Benadryl given for the relief of severe dysmenorrhea. Urticaria was produced by the medication, and cleared with the withdrawal of the drug. Reproduction of the lesions was not attempted. In answer to a questionnaire, concerning the production of eczema by the use of an antihistaminic drug, eight answers[95] failed to agree with the cited instance. None of these eight had noted the presence or association of eczematous lesions with the use of Benadryl or similar preparations. The same reference reveals a listing of the preferential medication used by several men over the country. Benadryl seemed to be the drug of choice where sedation was desired, whereas Hydryllin seemed to overshadow the others in the relief of symptoms of bronchial asthma. This reviewer sees little use for these drugs in asthma in competition with so many others of more valuable effect, unless there is an instance where the specific action of the antihistamine might be considered to be of some exact consequence.

Benadryl was used by Bignall and Crofton[6] in an effort to control streptomycin side effects. The nausea and vomiting was controlled in three test patients, but the giddiness was not relieved. Dramamine, as a preventative for motion sickness has been introduced rather recently. Gray and Carliner[13] found that this drug was beneficial upon testing its use on a large number of soldiers in transport. There were no toxic manifestations of consequence. The optimal dosage was 100 mg. four times daily. If the patients were too ill to retain the oral dosage, good relief was experienced with rectal administration. It is doubted if correct control was employed in the comparative results with the use of placeboes. Eight cases of acute nephritis were treated with Neo-Antergan by Craig, Clark and Chalmers.[24] They found that the symptoms of the disease were of shorter duration in the eight children treated than in the control, untreated group. When Pyribenzamine was discontinued an acute delirium cleared in the patient described by Lipp, Grug and Glenn.[73] The medication was originally given for drug dermatitis, but delusions and hallucinations were noted approximately forty-eight hours after the initial dosage. Perazil has been investigated by Jaros.[61] This drug in a dosage of 50 mg. daily, or twice daily, has been the source of some prolonged relief to the author's patients, even though it is not enteric-coated. Personal experience of this reviewer reveals that the drug was of distinct benefit in seasonal hay fever and less so in acute urticaria. Leopold[71] could find no marked change in the blood counts following the use of Benadryl for as long as seventeen months. No purpura nor hemorrhage occurred and readministration of the drug after a free period did not produce any further change. Intravenous injection of Benadryl produced no change of note with smaller dosages in the blood pressure of Mackmull's patients.[78] Dosages of 100, 200, and 300 mg. did tend to elevate the blood pressure and produce significant changes in the electrocardiographic tracings. These larger dosages should not be used in hypertensive patients. Blackman and Hayes[8] report a fatality with the use of Benadryl in the therapy of an acute attack of bronchial asthma. The primary cause of death was felt to have been a severe depression of the central nervous system with the drug being responsible for the depression. Benadryl decreased the size of the tuberculin reaction in the guinea pigs studied by Sarber.[106] The test animals were injected with serial dilutions of tuberculin before and after the administration of Benadryl which was continued throughout the forty-eight-hour period of delayed reaction. The incidence of necrosis was markedly reduced with the medication. The Mantoux test in humans was diminished during antihistamine therapy. Judd and Henderson[63] feel that encouraging results in human tuberculosis were obtained with this form of treatment. One wonders whether such a paper

should be given publicity or not, with the thought that a lay publication may gain the knowledge that rest, and other forms of accepted therapy need not be rigid. Spain and Pflum[116] report the findings of the Committee on Therapy of the American Academy of Allergy. Benadryl, Pyribenzamine, Neo-Antergan, Hydryllin and Trimeton were studied. Best results were reported in seasonal hay fever and urticaria. The committee advised against the substitution of these drugs in place of specific immunization or the use of epinephrine and ephedrine.

The use of the antihistaminic drugs in the aborting of common colds has received good publicity because of the inability of other measures to withstand the pressure of constant failure. Brewster[14] feels that the initial phase of a common cold is an allergic reaction. He studied 572 patients with symptoms characteristic of the common upper respiratory infection; nineteen or twenty-one patients were cured when the antihistaminic drug was given within one hour after the onset of initial symptoms; 116 patients (74 per cent) were cured when the drug was instituted within six hours of symptoms onset. The effectiveness of the therapy was inversely proportional to the lapse of time following the onset of symptoms to the initial dosage of the antihistaminic medication. Pyribenzamine was thought by Gordon[42] to be the best drug of three—Benadryl, Pyribenzamine, Thephorin—in aborting the symptoms of a common cold. Eighty-five per cent of 500 patients were made more comfortable and experienced shorter convalescent periods than did those untreated patients. The importance of these findings to the larger industries has been demonstrated by Murray.[86] He has noted 494 results of 510 treated patients; 314 of the 494 were cured in three days; eighty-three were improved with their symptoms having a duration of only six to seven days; ninety-seven patients received no benefit, and twenty-two of these failures possessed an idiosyncrasy for the Pyribenzamine used in therapy. Of the total treated, only seven missed any work, with the remainder being able to carry on their usual duties in spite of symptoms and treatment.

The necessity of careful interpretation of positive food tests in asthmatic children is discussed in an editorial.[33] Hill is quoted as stating that only about 20 per cent of positive tests are of clinical value and the importance of pollen and other environmental allergens demands much more attention in this regard. The relative importance of each positive reaction, inhalant or food, should be carefully appraised in the light of all accumulated findings in the individual problem. Uncommon reactions to uncommon foods are the subject of a paper by Langley.[67] He cites five case histories to show that some patients will respond in most unusual manners. His patients possessed clinical reactions to carrot and fish. Shock resulted from testing the first patient with an intradermal carrot extract. This should emphasize to all practicing allergists the danger of using the intradermal test without the protection of a previously administered scratch procedure. Langley's other patients demonstrated petit mal attacks from orange juice ingestion, from chocolate and celery use, and asthma of alarming degree from chocolate. Desensitization attempt by the oral route was a failure for this latter patient. A food discussion of gastrointestinal allergy with illustrative case reports is the basis of an article by Tuft.[125]

Though the general opinion is prevalent that allergy *per se* does not produce ulcer lesions, food allergy can provoke similar distress and symptoms. Where the x-ray evidence of ulcer is not demonstrable, food sensitivity must be differentiated from the organic pathology. It is recognized that there is considerable evidence in support of food allergy as a cause, actual and contributing, in irritable colon and mucous colitis. Even in chronic ulcerative colitis, the allergic factor cannot be overlooked, particularly if the history seems to point in that direction. Milk and wheat were thought by this author to be most frequently involved.

Vegetable gums in the etiology of allergic disorders may produce their results by ingestion, inhalation or contact. Gelfand[39] reports that the chief manifestations of

sensitivity are perennial rhinitis, asthma, dermatitis, urticaria and gastrointestinal distress. Karaya, tragacanth and arabic are the most important and most frequently used commercial gums. They are contained in certain foods to add bulk, thickness and binding qualities. Gum arabic is a common component of most adhesives, with gum tragacanth being used often in cosmetic and pharmaceutical manufacturing. Karaya is employed primarily in wave sets, hair dressings, and other lotions for external application. The widespread use of these gums makes it hazardous for the sensitive patient. The small bowel is believed by Tallant and his co-workers[121] to be involved in gastrointestinal food allergy. Upon feeding a special barium-allergen mixture to twelve patients, narrowing, segmentation and scattering were found in the small bowel on x-ray. Control patients were examined using a barium-water mixture. These bowel changes were not considered as specific but they were of significance in view of the normal pictures seen with the control feedings. Patients with allergic colitis do not have protruberant abdomens and are usually well nourished with no atrophy of the buttocks. The opinion of Lapin and Weissberg[68] is thus expressed in support of the use of sigmoidoscopic examination as an easy means of diagnosis. Seldom is hospitalization necessary for these patients. Three cases are reported in whom elimination diets and antihistaminic drugs were sources of palliative and prolonged relief. Price, Urbach et al[92] have shown excellent results with the use of propeptans in food allergy. Their findings are described in seven of ten patients with gastrointestinal symptoms due to sensitivity to ingested food. The three patients who failed to benefit from this method of therapy were thought to possess severe psychiatric disturbances. Under propeptan management, x-ray abnormalities of the gastrointestinal tract almost disappeared.

Davison[28] believes that when other methods of relief are adjudged failures, a course of histamine therapy is indicated in the migrainous patient. The intravenous route is to be preferred but this may be supplemented or replaced by the subcutaneous route if the former is impossible. Some patients have remained free of attacks for many months, and others have had a recurrence precipitated by allergic, physical or psychosomatic factors. Cunningham,[26] on the other hand, does not feel that histamine has been successful in his practice. Most of the patients he has seen with migraine have had their symptoms on a basis of allergy, until proven otherwise. The fact that histamine therapy is not a cure, but a procedure that must be given indefinitely is disturbing to this author. All other physical and organic factors should first be ruled in or out before any decision as to the cause of the migraine attacks has been ascertained. The value of thorough skin testing in the search for relief in migraine has been given impetus by King.[66] He has described a patient with recurrent, typical migraine in whom strict dietary management—based on the results of skin tests—and dust therapy has been successful in aborting and preventing the incapacitating attacks. Ogden[87] published six case reports wherein the headaches were due to dust sensitivity and adequate therapy was responsible for good relief. Most of his patients had been long in the use of nasal medication for the relief of associated nasal symptoms. Grenfell[45] has used nicotinic acid to relieve fifteen patients with typical migraine seizures. This medication was given thirty-one times to these patients and was successful in thirteen occasions. No toxic manifestations were encountered and no change was noted in blood pressure nor pulse either during or after the administration. For this reason, complicating heart or vascular disease was not a contraindication to the therapy. No attempt was made nor considered to prevent recurrences of the attacks. Marcussen and Wolff[81] feel that the therapy of migraine resides in two categories: treatment of the individual and prevention of further complaints. Intracranial vasoconstriction is considered as pre-headache phenomena with the onset of the headache being associated with vasodilation. The best method of attack-relief was thought to be ergotamine tartrate. The removal of stress seemed to reduce the frequency of attacks inasmuch

as emotional reactions, fatigue and accumulated tension added up to the typical parade of symptoms called migraine. That the above authors may misunderstand the true mechanism of the attack of migraine has been suggested by Waldbott.[120] He thinks that a pure psychoneurotic approach to this question is misleading. His letter has complained of the lack of consideration and mention of allergy in the above article on migraine. Friedman, Brenner and Carter[37] express themselves that trauma and psychoneurosis are the two most common causes of chronic headache. They reported 521 patients, with 494 receiving combined psychotherapy and pharmacotherapy and twenty-seven treated with psychotherapy alone. Of the drugs used, the analgesics were determined to be most efficacious. Because of the similarity of results from drug therapy, the authors suggest that the above two common types of chronic headache are closely related as to causative mechanisms.

A very good description of the attacks with the history of the headaches is considered of the utmost importance by Horton.[57] For example, the time of onset is of the greatest significance. Night attacks are typical of histamine cephalalgia. Pain in the head arises from the following sources: the tissues covering the cranium, cranial periosteum and endosteum, and certain intracranial structures. The cranium, brain, dura, pia-arachnoid, choroid plexus and ependymal lining of the ventricle are insensitive to pain. Practically all headaches, regardless of type, are vascular in origin. Sixteen illustrative case reports are given as examples of the various types of headaches, with notes indicating the proper diagnostic and therapeutic approach for each occasion. This same author, with Macy,[77] lists the five fundamental features of migraine: periodicity, cephalalgia, gastrointestinal disturbances, cortical changes and a positive familial history of migraine attacks. Two series of a total of 144 cases are reviewed to establish the effect of histamine therapy. Most improvement was noted in the atypical cases of migraine—those in whom a periodic cephalalgia is associated with any of the above three factors. Combined subcutaneous and intravenous therapy was most beneficial. Recurrence of symptoms following treatment was the rule unless therapy was continued. Hansel[49] feels that Cafergone, a combination of ergotamine tartrate (1 mg.) with caffeine (100 mg.) is superior to the use of the former preparation by itself. The medication is available for oral usage. Cafergone was found to be effective in the relief of all types of headache, especially in the atypical and typical histaminic cephalalgia. Gynergen was thought to be superior, however, for the relief of the acute attack, if it could be given at the onset of symptoms. Ireland[60] has reported 199 cases of Ménière's disease, with ninety of them being treated with resection of the eighth nerve. Destruction of the labyrinth was done in thirty-three patients. Though both methods were beneficial, medical management consisting of sedation, sodium restriction, and limitation of fluid intake gave satisfactory relief in about 90 per cent of the cases. Histamine therapy was of some value, relieving nine of eleven patients.

This review of miscellaneous literature in allergy would hardly be complete without calling attention to the listing compiled by Bowen and Efron.[11] This is of importance because of the great consumption of acetylsalicylic acid and the frequency with which this use is encountered in allergy.

REFERENCES

1. Ashley, R. E.: Allergy in otolaryngology. Laryngoscope, p. 686, 1948.
2. Barnet, E. G.: Internat. Corr. Club Allergy, series XI, p. 27.
3. Bernton, H. S.; Coulson, E. J., and Stevens, H.: On allergy to cottonseed oil. J.A.M.A., 140:869, 1949.
4. Bernton, H. S.: Transcript of Official Record, pages 14589-14855 (pages 64-83 in transcript) —Testimony on "Corn Allergics," Docket No. FDC 31 (b).
5. Bieberdorf, F. W., and Argabrite, J. W.: Extracts of molds grown on synthetic media. J. Allergy, 20:50, (Jan.) 1949.
6. Bignall, J. R., and Crofton, J.: Antihistaminic drugs in the treatment of nausea and vomiting due to streptomycin. Brit. M. J., 1:13, 1949.
7. Black, W. B.: Allergy in otolaryngology. Laryngoscope, p. 686, 1948.
8. Blackman, N. S., and Hayes, J. C.: Fatality associated with Benadryl therapy. J. Allergy, 19:390, 1948.

9. Blanton, W. B., and Sutphin, A. K.: Death during skin testing. Am. J. M. Sc., 217:169, 1949.
10. Bowen, Ralph: Cottonseed oil—post-mortem. Internat. Corr. Club Allergy, series XI, p. 138.
11. Bowen, R., and Efron, H. G.: Internat. Corr. Club Allergy, series XI, p. 45.
12. Braden, A. H.: Internat. Corr. Club Allergy, series XI, p. 69.
13. Brenneman, R. E.: Management of anesthesia for the allergic patient. Ann. Allergy, 7:534, (July-Aug.) 1949.
14. Brewster, J. M.: Antihistamine drugs in the therapy of the common cold. U. S. Nav. M. Bull., 49:1, 1949.
15. Bullen, S. S., Sr.: What should the general practitioner do about allergy? J.A.M.A., 140: (May) 1949.
16. Cazort, A. G.: Internat. Corr. Club Allergy, series XI, p. 43.
17. Cazort, Alan G.: Transcript of Official Record, pages 14589-14855 (pages 83-94 in transcript) —Testimony on "Corn Allergies," Docket No. FDC 31 (b).
18. Clein, N. W.: Allergy and the tonsil problem in children. Ann. Allergy, 7:329, (May-June) 1949.
19. Cohen, M. B., and Abram, L. E.: Cases illustrating some causes for failure in the management of patients with allergy. Ohio M.J., 45:561, 1949.
20. Cohen, V. L., and Fisher, W. J.: An evaluation of radium treatment to the nasopharynx in asthmatic children. J. Allergy, 20:328, 1949.
21. Cole, H. N., Jr.; Marmelzat, W. L., and Walker, A. E.: Severe allergic sensitization of an estrogenic cream. Ohio M.J., 44:472, 1948.
22. Cooke, R. A.: The allergy factor in disease. Ann. Int. Med., 31:17, (July) 1949.
23. Coppinger, W. R., and Goldner, M. G.: Fatal anaphylactic shock following the administration of a protein digest (Amigen). J. Allergy, 20:369, (Sept.) 1949.
24. Craig, J.; Clark, N. S., and Chalmers, J. D.: Antihistamine drug treatment of acute nephritis. Brit. M.J., 1:6, (Jan.) 1949.
25. Criep, Leo.: Collagen disease. Its relation to hypersensitiveness. J. Allergy, 20:116, (March) 1949.
26. Cunningham, T. D.: Internat. Corr. Club Allergy, series XI, p. 173.
27. Davison, F. W.: Bronchopulmonary infection in allergic individuals. Ann. Otol., Rhin. & Laryng., 57:884, 1948.
28. Davison, H. M.: Internat. Corr. Club Allergy, series XI, p. 172.
29. Detwiler, H. K.: Management of food allergy. Modern Med., 17:82, 1949.
30. Duff, G. L.: The diffuse collagen diseases. A morphological correlation. Canad. M.A.J., 58:317, 1948.
31. Editorial: Graduate education in allergy. Ann. Int. Med., 30:1301, (June) 1949.
32. Editorial: Ann. Allergy, 6:440, 1948.
33. Editorial: Ann. Allergy, 6:598, 1948.
34. Eisenstadt, W. S.: The incidence and significance of molds in allergic respiratory symptoms. Lancet, 68:217, 1948.
35. Estrada, de la Riva, G.: Contribution to the study of tropical eosinophilia. South. M. J., 42:429, (May) 1949.
36. Figley, Karl: Sensitivity to edible vegetable oils. J. Allergy, 20:198, (May) 1949.
37. Friedman, A. P.; Brenner, C., and Carter, S.: Chronic headache. J.A.M.A., 139:195, 1949.
38. Gelfand, M. L., and Aronoff, S.: Periarteritis nodosa—possible relation to the increased use of sulfonamides. Ann. Int. Med., 30:919, (May) 1949.
39. Gelfand, H. H.: The vegetable gums by ingestion in the etiology of allergic disorders. J. Allergy, 20:311, 1949.
40. Glaser, J.: Internat. Corr. Club Allergy, series XI, p. 182.
41. Glaser, J.: J. Allergy, 15:283, 1944 (quoted in Reference 40).
42. Gordon, J. S.: Antihistamine drugs in the treatment of upper respiratory tract infections. Laryngoscope, 58:1265, (Dec.) 1948.
43. Gray, L., and Carliner, P.: The prevention and treatment of motion sickness. Bull. Johns Hopkins Hosp., 84:5, 1949.
44. Green, Mayer A.: Aerosol penicillin in allergic patients with respiratory infections. Ann. Int. Med., 31:260, (Aug.) 1949.
45. Grenfell, R. F.: Treatment of migraine and nicotinic acid. Am. Practitioner, 3:542, 1949.
46. Halpin, L. J.: Transcript of Official Record, pages 14589-14855 (pages 100-104 in transcript) —Testimony on "Corn Allergies," Docket No. FDC 31 (b).
47. Hansel, F. K.: Internat. Corr. Club Allergy, series XI, p. 29.
48. Hansel, F. K.: Allergy in otolaryngology. Laryngoscope, p. 652, 1948.
49. Hansel, F. K.: The treatment of headache. Ann. Allergy, 7:155, (March-April) 1949.
50. Hansen-Pruss, O. C.: Studies of drug sensitivity. Ann. Allergy, 7:219, (March-April) 1949.
51. Harkavy, Jos.: Allergic factor in gout. J.A.M.A., 139:75, 1949.
52. Harrell, J. A.: Recognition and management of allergic conditions by otorhinolaryngologists. North Carolina M. J., 10:75, 1949.
53. Harris, J. F., and Laws, C. L.: Periarteritis nodosa. Ann. Allergy, 7:105, (Jan.-Feb.) 1949.
54. Harris, H. L.: Therapeutic effects of certain antihistamine drugs in allergic conditions. Ann. Allergy, 7:206, (March-April) 1949.
55. Hauntz, E. A., and Grinnell, E. L.: Sensitivity reactions from penicillin preparations of prolonged action. Ann. Allergy, 7:4, 1949.
56. Hill, L. W.: An evaluation of therapy in infantile eczema. J.A.M.A., 140:139, 1949.
57. Horton, B. T.: Headache, clinical varieties and therapeutic suggestions. M. Clinics North America, 33:973, (July) 1949.
58. Hult, H., and Jorpes, E.: Is insulin antigenic? Lancet, Cond., 1:780, 1949.
59. Hurvitz, P.: Antistine in ocular allergy. Am. J. Ophth., 31:1409, (Nov.) 1948.
60. Ireland, P. E.: The diagnosis and treatment of Meniere's symptom complex. Canad. M.A.J., 58:269, 1948.
61. Jaros, S. H.: The clinical application of a new piperazine compound. Ann. Allergy, 7:466, (July-Aug.) 1949.
62. Jones, E. H.: Internat. Corr. Club Allergy, series XI, p. 35.
63. Judd, A. R., and Henderson, A. R.: The use of antihistamines in human tuberculosis. Ann. Allergy, 7:306, (May-June) 1949.
64. Ketcham, W. M.: Allergy. A new concept in treatment. J. Missouri M. A., 45:896, 1948.
65. King, F. K.: Protracted course in periarteritis nodosa. J. Mt. Sinai Hosp., 15:97, 1948.
66. King, L. J.: Internat. Corr. Club Allergy, series XI, p. 59.
67. Langley, W. D.: Uncommon reactions to uncommon foods. Ann. Allergy, 6:684, 1948.

68. Lapin, J. H., and Weissberg, W. W.: Sigmoidoscopy in diagnosis of allergic colitis. Am. J. Dis. Child., 76:78, (July) 1948.
69. Leider, M. L., and Baer, R. L.: The present status of passive transfer antibodies in allergic eczematous contact-type dermatitis. J. Invest. Dermat., 10:425, 1948.
70. Leider, M., and Furman, D.: Allergic eczematous contact-type dermatitis from odd things or in odd ways. Ann. Allergy, 6:693, 1948.
71. Leopold, H. C.: The absence of the effects of Benadryl on the hematopoetic system. Ann. Allergy, 7:510, 1949.
72. Levin, R.: The role of fungi in inhalant allergy. Am. J. M. Technol., 15:2, (Jan.) 1949.
73. Lipp, G. M.; Ting, E. S., and Glenn, H. R.: A case report of drug delerium interpreted as being due to pyribenzamine. Journal Lancet, 68:342, 1948.
74. Loveless, Mary: Six histamine antagonists in hay fever with a review of the literature. J. Am. M. Womens A., 4:105, 1949.
75. McAllister, R. M., and Hecker, A. O.: The incidence of allergy in psychotic reactions. Am. J. Psychiat., 105:843, 1949.
76. McGee, W. A.: Pediatric allergy. Wisconsin M.J., 48:229, 1949.
77. Macy, D., Jr., and Horton, B. T.: Treatment of migraine with histamine. Review of 144 cases. J.A.M.A., 137:1110, 1948.
78. Mackmull, G.: The influence of intravenously administered Benadryl on blood pressure and electrocardiograms. J. Allergy, 19:36, 1948.
79. Maietta, A. L.: Relief of asthmatic seizures with micronized epinephrine, 1-1,000. J. Maine M. A., 40:108, 1949.
80. Mahnros, H., and Hermer, H.: Treatment of pernicious anemia with special reference to hypersensitivity to liver extract. Nord. med., 40:2133, 1948.
81. Marenssen, R. M., and Wolff, H. G.: Therapy of migraine. J.A.M.A., 139:198, 1949.
82. Markan, H.; Jacobi, M.; Ravcoff, H.; Kagut, P., and Auerbach, R. W.: Effect of intravenously administered oxygen on symptoms and vital capacity in bronchial asthma. Ann. Int. Med., 29:607, (Oct.) 1948.
83. Meyer, M. G.: Nonreaginic allergy. Ann. Allergy, 6:417, (July-Aug.) 1948.
84. Miller, J.: Allergic arthritis. Ann. Allergy, 7:497, (July-Aug.) 1949.
85. Mullinger, M. A., and Bogoch, A.: Cold hypersensitivity. Canad. M.A.J., 58:499, 1948.
86. Murray, J. G.: The treatment of head colds with an antihistaminic drug. Indust. Med., 18:215, (May) 1949.
87. Ogden, H.: Inhalant sensitization in allergic headaches. South. M.J., 41:931, 1948.
88. Parker, H. L., and Kernohan, J. W.: The central nervous system in periarteritis nodosa. Proc. Staff Meet., Mayo Clin., 24:17-52, 1949.
89. Perlman, H. H.: Undecylinic acid given orally in psoriasis and neurodermatitis. A preliminary report. J.A.M.A., 139:444, 1949.
90. Phillips, E. W.: Clinical evidence of sensitivity to gonadotropine in allergic women. Ann. Int. Med., 30:364, (Feb.) 1949.
91. Pincus, George: Internat. Corr. Club Allergy, series XI, p. 15.
92. Price, A. H.; Urbach, F., et al: Propentan therapy for gastrointestinal food hypersensitivity. Am. J. Digest Dis., 16:161, (May) 1949.
93. Prickman, L. E.: General principles of allergy and hypersensitivity. Proc. Staff Meet., Mayo Clin., 24:429, 1949.
94. Prince, H. E., et al: Mold fungi in the etiology of respiratory allergic disease, IX. Further studies with mold extracts. Ann. Allergy, 7:310, (May-June) 1949.
95. Questionnaire Results: Internat. Corr. Club Allergy, series XI, p. 110.
96. Rackemann, F. M.: Allergy, a review of the literature, 1946-47. Arch. Int. Med., 81:696, 1948.
97. Ralston, D. E., and Kvole, W. T.: The renal lesions of periarteritis nodosa. Proc. Staff Meet., Mayo Clin., 24:17-52, 1949.
98. Randolph, T. G.: Transcript of Official Record, pages 14589-14855 (pages 1-59 in transcript) —Testimony on "Corn Allergies," Docket No. FDC 31 (b).
99. Ratner, B.: Management of the pre-allergic child. Ann. Allergy, 6:629, (Nov.-Dec.) 1948.
100. Rawlings, F. F. A.: Transcript of Official Record, pages 14589-14855 (pages 107-125 in transcript)—Testimony on "Corn Allergies," Docket No. FDC 31 (b).
101. Reiser, M. F., and Ferris, E. B.: Observations on the use of the respirator in refractory status asthmaticus. Ann. Int. Med., 29:64, (July) 1948.
102. Rockwell, G. E.: The role of allergy in rheumatic arthritis and a suggested treatment. Preliminary report. Ann. Allergy, 7:195, (March-April) 1949.
103. Rosen, F. L.: Sensitivity to s[illegible] shock with recovery following an intracutaneous test. J.A.M.A [illegible]
104. Salmon, P.: Present-day aspect [illegible] Hosp. J., 6:207, (Oct.) 1948.
105. Samitz, M. H., and Horvath, P. N.: Observations on severe penicillin reactions. Ann. Allergy, 7:490, (July-Aug.) 1949.
106. Sarber, R. W.: Effect of Benadryl Hydrochloride on the tuberculin reaction in guinea pigs. Am. Rev. Tuberc., 57:504, 1948.
107. Schenck, H. P.: Effects of Allergy on the ethmoid sinuses. Arch. Otolaryng., 49:48, (Jan.) 1949.
108. Schutzbank, F. B.: Climato-therapy in allergic disease. J.A.M.A., 139:1260, 1949.
109. Schilling, M. D.: Internat. Corr. Club Allergy, series XI, p. 54.
110. Sheldon, J.; Schreiber, E. O., and Lovell, R. G.: Hereditary angioneurotic edema, with a case report. J. Lab. & Clin. Med., 34:524, 1949.
111. Sheldon, John: Internat. Corr. Club Allergy, series XII, p. 139.
112. Sherman, W. B.: Drug allergy. J.A.M.A., 140:447, 1949.
113. Simon, Frank: Clinical allergy. J.A.M.A., 139:1258, 1949.
114. Simon, F. A.: A study of atopic eczema. Ann. Allergy, 6:584, (Sept.-Oct.) 1948.
115. Spain, W. C.: Importance of allergy in ear, nose and throat conditions. Laryngoscope. 58:1299, 1948.
116. Spain, W. C., and Pflum, F. A.: An evaluation of the present status of antihistamine substances. New York State J. Med., 48:2272, 1948.
117. Stenbuck, F. A.: Internat. Corr. Club Allergy, series XI, p. 80.
118. Sterling, A.: Fishman, A. E., and Sharoes, F.: Massive doses of Penicillin in chronic asthmatics. Am. Practitioner, 2:570, 1948.
119. Stevenson, I. P.: Therapeutic effect of the climate of Arizona. Arch. Phys. Med., 28:644, 1947.
120. Sweeney, A. R., Jr., and Baggenstoss, A. H.: Pulmonary lesions of periarteritis nodosa. Proc. Staff Meet., Mayo Clin., 24:17-52, 1949.

121. Tallant, E. J.; O'Neill, H. A., et al: Gastrointestinal food hypersensitivity: a roentgenographic demonstration. Am. J. Digest. Dis., 16:140, 1949.
122. Testimony: Allergy to cottonseed and other oilseeds and their edible derivatives. Published by National Cottonseed Products Assoc. Inc., Memphis, Tenn.
123. Thomas, E. W.; Landy, S., and Cooper, C.: Reactions to penicillin therapy for syphilis. J. Invest. Dermat., 10:77, 1948.
124. Tuft, L.: Importance of inhalant allergens in atopic dermatitis. J. Invest. Dermat., 12:211, 1949.
125. Tuft, L.: Allergy as a factor in gastrointestinal disorders. Rev. Gastroenterol., 16:209, 1949.
126. Turnbull, J. A.: Some observations on allergy of the respiratory tract. Am. J. Digest Dis., 16:132, (April) 1949.
127. Turner, H. H.: The effect of aminophylline on urticarial skin reactions. J. Allergy, 20:307, 1949.
128. Underwood, G. B., and Gaul, L. A.: Overtreatment dermatitis in dermatitis venenata due to plants. J.A.M.A., 138:570, 1948.
129. Waldbott, Geo.: Migraine. J.A.M.A., 139:734, 1949.
130. Wold, L. E., and Baggenstoss, A. H.: Gastrointestinal lesions of periarthritis nodosa. Proc. Staff Meet., Mayo Clin., 24:17-52, 1949.
131. Wolf, A. .: Internat. Corr. Club Allergy, series XI, p. 13.
132. Zeller, M.: Rheumatoid arthritis—food allergy as a factor. Ann. Allergy, 7:200, (March-April) 1949.
133. Zolov, B.: Clinical evaluation of pyrrolazote and orthoxine in allergic disease. J. Maine M. A., 40: 105, (May) 1949.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA

(Continued from Page 784)

part of face, the anterior and posterior portions of the chest, the axillary regions, abdomen, back and in the right inguinal region. He felt better, ate some food and became cheerful. A heavy mucoid material was discharged from both nostrils. His progress continued steadily. Ephedrine, aminophylline and codeine administered orally were sufficient. The subcutaneous emphysema disappeared slowly; that in the inguinal region persisted for seventeen days, and the axillary and supraclavicular areas persisted for ten to fourteen days.

SUMMARY

1. Two cases of subcutaneous emphysema complicating an acute exacerbation of bronchial asthma are reported.

2. Recovery followed bed rest and symptomatic management.

3. The severe symptoms of asthma abated with the occurrence of the subcutaneous emphysema.

REFERENCES

1. Faulkner, William B., and Wagner, R. J.: Fatal subcutaneous pneumothorax and subcutaneous emphysema in an asthmatic. J. Allergy, 8:267, (March) 1937.
2. Francis, Nathan: Subcutaneous emphysema during asthma. Ann. Allergy, 2:342, (July-Aug.) 1944.
3. Peterson, Heyes: A fatal case of bronchial asthma complicated by mediastinal and subcutaneous emphysema. J. Allergy, 18:413, (Nov.) 1947.
4. Schwartz, Emanuel: Spontaneous mediastinal and subcutaneous emphysema complicating bronchial asthma. J. Allergy, 16:279, (Nov.) 1945.
5. Unger, Leon: Bronchial Asthma. Springfield: Charles C Thomas, 1945.

News Items

INTERNATIONAL ASSOCIATION OF ALLERGISTS

The following societies are official members of The International Association of Allergists:

SOCIEDAD ARGENTINA DE ALERGIA: President, Dr. Miguel Agustin Solari, Carlos Pelegrini 1219, Buenos Aires, Argentina.

SOCIETE BELGE DE L'AALERGIE: President, Prof. Dr. Paul Bordet, 28 Rue du Remorqueur, Bruxelles, Belgium.

SOCIEDADE BRASILEIRA DE ALERGIA: President, Dr. Nelson Passarelli, Rua Alvaro Alvim No. 31, Sala 301, Rio de Janeiro, Brazil.

SOCIEDAD CHILENA DE ALERGIA: President, Dr. Eduardo Diaz Carrasco, Arturo Prat 72, Santiago, Chile.

SOCIEDAD COLOMBIANA DE ALERGIA: President, Dr. M. Sanchez Medina, Calle 22, No. 12-13, Bogota, Colombia.

CUBAN ALLERGY SOCIETY: President, Dr. Gonzalo Estrada de la Riva, L Y 25, Vedado, Habana, Cuba.

BRITISH ASSOCIATION OF ALLERGISTS: President, Dr. Vera B. Walker, 24 Beaumont Street, Oxford, England.

HUNGARIAN SECTION OF ALLERGISTS: President, Prof. Dr. K. Hajos, Muzeum krt, 39, Budapest, IV, Hungary.

ASSOCIAZIONE ITALIANA PER LO STUDIO DELL'ALLERGIA: Honorary President, Prof. Dr. Cesare Frugoni, 47 Via Bruzelles, Roma, Italia.

SOCIEDAD PERUANA DE ALERGIA: President, Alberto Flores, M.D., Av. La. Colmena 216, Lima, Peru.

SOCIEDAD ESPANOLA DE ALERGIA: President, Dr. O. Jimenez Diaz, General Mola 9, Madrid, Espana (Spain).

SOUTHERN SWEDISH ALLERGY FORUM: Chairman, Prof. Gösta Dohlman, Dept. of Otolaryngology, Lund University Hospital, Lund, Sweden.

SWEDISH ASSOCIATION OF ALLERGISTS: President, Prof. Sven Hellerstrom, Karolinska Sjukhuset, Stockholm 60, Sweden.

SWISS ALLERGY SOCIETY: President, Prof. Dr. A. S. Grumbach, Hygiene-Institut der Universitat, Gloriastr. 32, Zurich 7, Switzerland.

THE AMERICAN COLLEGE OF ALLERGISTS: President, Dr. Jonathan Forman, 956 Bryden Road, Columbus, Ohio.

THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY: President, Dr. Rea E. Ashley, 384 Post Street, San Francisco, California.

SOUTHEASTERN ALLERGY ASSOCIATION

The fifth annual meeting of the Southeastern Allergy Association will be held at the Columbia Hotel, Columbia, South Carolina, on Saturday and Sunday, February 11 and 12, 1950. Please note that the month has been changed because of changes made in the meeting dates of the American Academy of Allergy and the American College of Allergists. This puts the meeting of the Southeastern Allergy Association midway between the two.

The guest speakers will be Dr. Jonathan Forman, President of the American College of Allergists, and Dr. Theodore Squier, President-Elect of the American Academy of Allergy.

In view of the popularity of panel discussions, there will again be two, one on "Pediatric Allergy" with Dr. Lewis Hoppe of Atlanta as co-ordinator, and the

other on "Office Procedure" with Dr. J. Warrick Thomas of Richmond as coordinator.

Members who are desirous of presenting papers at this meeting are urged to contact the secretary at an early date. Each paper will be allowed 20 minutes for presentation and 10 minutes for discussion.

For further information, please write directly to the Secretary, Dr. Katharine Baylis MacInnis, 1515 Bull Street, Columbia, South Carolina.

NEW YORK ALLERGY SOCIETY AWARD

The Committee on Annual Award of the New York Allergy Society, Horace S. Baldwin, Chairman, announces a prize of $150.00 for the best essay of merit by a student of a medical school in Greater New York City. For the coming year 1949-1950, the topic selected by the Annual Award Committee is "Bronchial Asthma and its Relation to Foci of Infection in the Upper Respiratory Tract." The essay should not exceed 15,000 words. It should contain some reference to clinical experience gained in the medical school or hospital, and references to published work should be indicated in a Bibliography. It should be approved by the head of the department of medicine of the medical school in which the essayist is a student.

A report of original investigations in the fields of general allergy or of immunology, which the committee deems meritorious, will be given consideration equal to that of essays on the designated topic.

All essays must be sent to the Secretary of the New York Allergy Society, Dr. Frederick R. Brown, 39 West 55th Street, New York City prior to May 1, 1950.

PENNSYLVANIA ALLERGY ASSOCIATION

The fall meeting of the Pennsylvania Allergy Association was held in Pottsville, Pennsylvania, with Drs. Harold Abramson, James Flood, Bret Ratner, Harry Rogers, and Alexander Peters as the guest speakers. The following officers were elected for the ensuing year: President, Dr. Alexander Peters of Allentown; Vice President, Dr. Samuel Kaufman of Wilkes-Barre; Secretary-Treasurer, Dr. Ralph M. Mulligan of Reading. Drs. Lester Fowle of Lewisburg and James Mansmann of Pittsburgh were elected to the Board of Regents for a three-year term. Dr. Stephen Lockey of Lancaster was awarded the first Certificate of Merit for the most outstanding work in Allergy during the year 1949. Thirteen new members were elected to membership at this meeting.

The spring meeting of the Association will be held at the Bedford Springs Hotel in Bedford, Pennsylvania, on May 11, 1950. The spring meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held at the same place on May 12, 13, and 14.

PHILADELPHIA ALLERGY SOCIETY

The Fifteenth Annual Scientific Meeting of the Philadelphia Allergy Society was held on October 26, 1949. Dr. Herman Gold, President, presided, with Dr. Samuel E. Rynes as Secretary. The following program was presented:

1. "The Prevention of Infectious Asthma" by A. E. Fishman, M.D.
2. "Inhalant Allergens as a Factor in Atopic Dermatitis. An Experimental Clinical Study," by Louis Tuft, M.D., Harold S. Tuft, M.D., and V. Muriel Heck, M.T.
3. "Dermatitis Venenata Due to Verbena Rigida Spreng" by Charles Bancroft, M.D.
4. Panel Discussion on Antihistamines in the 1949 Hay Fever Season. Trimeton, Decapryn, and Pyrrolazote by Alexander Sterling, M.D., Pyribenzamine and

Neo-Antergan by George Blumstein, M.D. Neohetramine by Louis Silcox, M.D. Chlor-Trimeton Maleate by Samuel E. Rynes, M.D.

5. "Roentgenographic Appearance of the Chest in Diseases Affecting the Peripheral Pulmonary Vessels," by Robert Phelps Barden, M.D., Assistant Professor of Radiology in the School of Medicine at the University of Pennsylvania.

CHICAGO SOCIETY OF ALLERGY

At a recent meeting of the Chicago Society of Allergy, the following officers were elected for the ensuing year: President, Dr. Morris A. Kaplan; President-Elect, Dr. Townsend B. Friedman; and Secretary-Treasurer, Dr. Theron G. Randolph.

NEW EQUIPMENT

A machine for cleaning hypodermic needles is now being manufactured and marketed by the Medical Equipment Laboratories, 5404 Sierra Vista Avenue, Los Angeles 38, California.

The Casady Hypodermic Needle Cleaner, invented by R. R. Casady, M.D., was developed to reduce the great amount of time now required for the manual cleaning of the ever increasing number of hypodermic needles being used. Equally important—it gives dependably clean needles.

This machine can cut the amount of time required to clean needles by as much as 80 per cent—and can deliver needles more thoroughly and effectively than is possible by hand methods.

In this machine the hubs of the needles are forcefully cleaned by an electrically driven swab. Then the needles are washed with three separate fluids, successively passed through the needles under 20 pounds pressure, followed by a stream of compressed air, leaving them dry and clean.

One hundred needles can be swabbed out, washed, rinsed and dried in nine minutes.

* * *

Philip M. Gottlieb, M.D., F.A.C.A., announces the removal of his offices for the practice of Allergy and Internal Medicine to 818 Medical Arts Building, Philadelphia 3, Pennsylvania.

* * *

As the ANNALS goes to press, we regretfully announce the deaths of two Fellows of the College—Dr. W. Byron Black, Kansas City, Missouri, who was President of the Hansel Foundation, and Dr. Arthur C. Kalisch, York, Pennsylvania, who was one of the charter members of the Pennsylvania Allergy Association. Their obituaries will appear in the January-February issue of the ANNALS.

* * *

ANNALS OF ALLERGY, 7:301-442 (May-June) 1949, was indexed in part under Current Medical Literature of the JAMA 141:796 (November 12) 1949 issue. The article by Judd and Henderson, "Use of Antihistaminic Drugs in Human Tuberculosis: Preliminary Report," and "Allergy and the Tonsil Problem in Children" by Clein were abstracted.

* * *

Dr. Harold A. Abramson has been appointed Chief of the Allergy Clinic at The Mount Sinai Hospital, New York, New York.

BOOK REVIEWS

PAVLOV, A BIOGRAPHY. By B. P. Babkin, M.D. 378 pages. Illustrated. $6.00. The University of Chicago Press.

The major and fundamental contributions of Pavlov to medicine are well known to all serious students of gastroenterology, neurology and psychiatry. Pavlov's fame, however, rests on a wider and more fundamental base than the mass accumulation of data because the principles and methods of scientific investigation which he established are of enduring importance and significance. This biography amply satisfies a long felt need for an authentic description of Pavlov as a man, the environment in which he worked and a critical summation of his contributions to medicine.

Professor Babkin, now of the Montreal Neurological Institute, is without doubt best qualified to write such a biography because he worked with Pavlov for many years, and has himself attained such eminence as a scientist in his own right that he is justly considered the most famous of Pavlov's students. One would therefore expect such an author to write a creditable biography. Professor Babkin has done much more than this. He has written such a masterful exposition that his text might well serve as an example to other biographers of scientists.

Many facts of Pavlov's personal life are here presented for the first time. His relations with his colleagues and contemporaries are described impartially with revealing and amusing anecdotes. The sections summarizing and analyzing Pavlov's work, and showing its impact on Pavlov's contemporaries as well as its influence on present day scientists, are particularly well done.

This book is enjoyable and profitable reading for any intelligent layman. It deserves careful reading by everyone who has an interest in the medical sciences. It is required reading for every physician who seeks an understanding of his own profession and the role of Pavlov's monumental contributions.

SKIN SENSITIZATION TO BAL OINTMENT

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4. Holley, Howard L.: The use of BAL (2, 3-dimercaptopropanol) in the treatment of agranulocytosis following intensive arsenotherapy for syphilis. Ann. Int. Med., 27:231-238, (Aug.) 1947.
5. Longscope, W. T., and Luetscher, J. A., Jr.: The treatment of acute mercury poisoning by BAL. J. Clin. Investigation, 25:557, 1946.
6. Margolis, H. M., and Caplan, P. S.: BAL in the treatment toxicity from gold. Ann. Int. Med. 27:353-360, (Sept.) 1947.
7. Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: British anti-lewisite (BAL). Nature, 156:601 and 616, 1945.
8. Sulzberger, M. B., and Baer, R. L.: The Year Book of Dermatology and Syphilology. p. 28. Chicago: The Year Book Publishers, Inc., 1946.
9. Sulzberger, M. B., and Baer, R. L.: Development and use of BAL. J.A.M.A., 133:295, 1947.
10. Sulzberger, M. B.: Baer, R. L., and Kanof, A.: Clinical uses of 2, 3-dimercaptopropanol (BAL). V. Skin sensitization to BAL. J. Clin. Investigation, 25:488, 1946.

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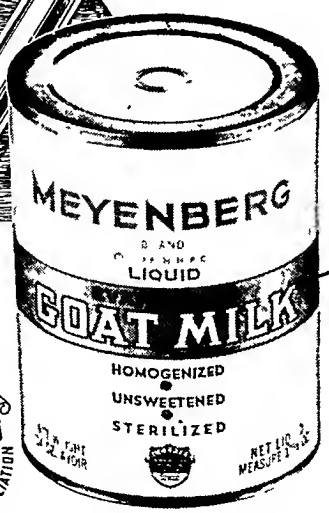

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1. PERSKY, A. H.: "Penicillin-Vasoconstrictor Treatment of Post-Influenzal Rhinitis and Sequellae", Medical Record, November, 1947.

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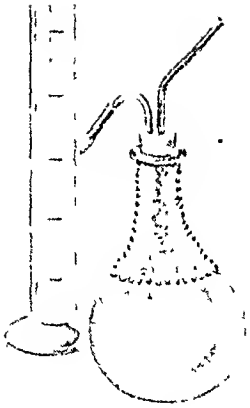

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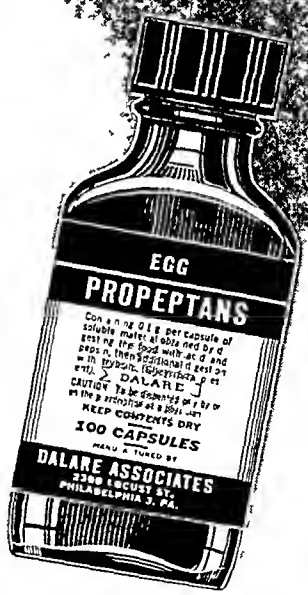

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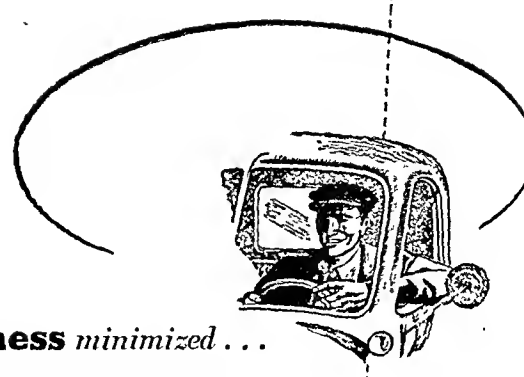

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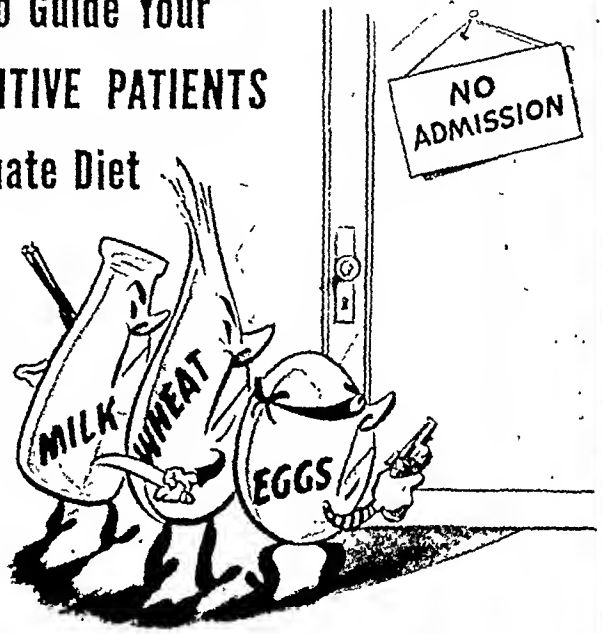

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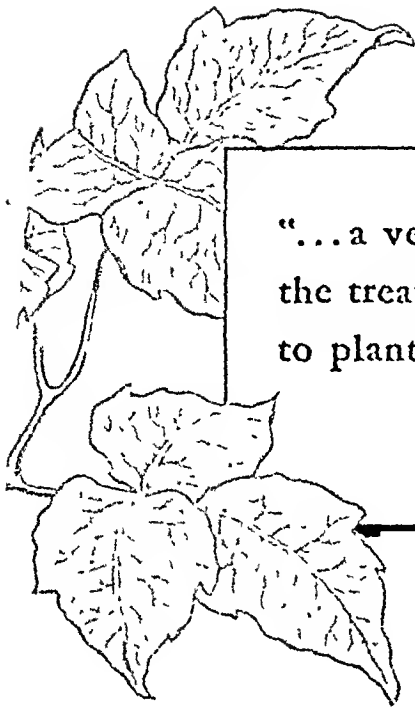

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1. Carrier, R. E., Krug, E. S., and Glenn, H. R.: J. Lancet, 68: 240, June 1948.
2. Feinberg, S. M. and Bernstein, T. B.: J. of A.M.A., 134: 10, July 1947.

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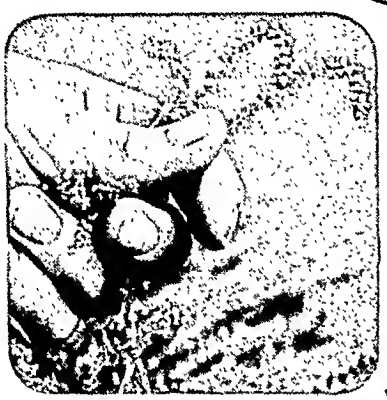

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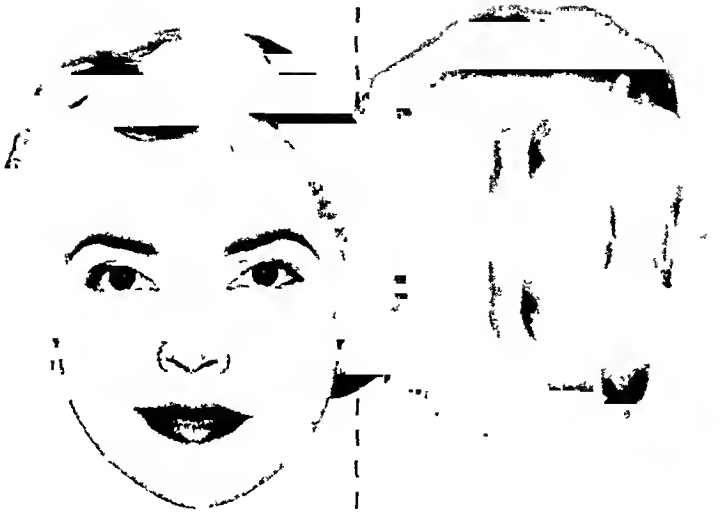

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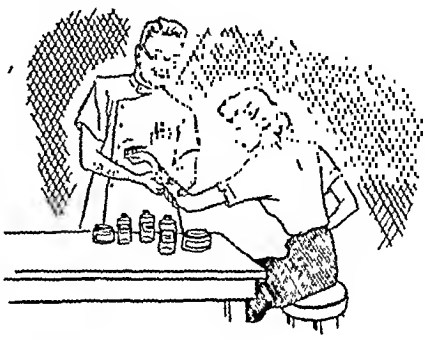

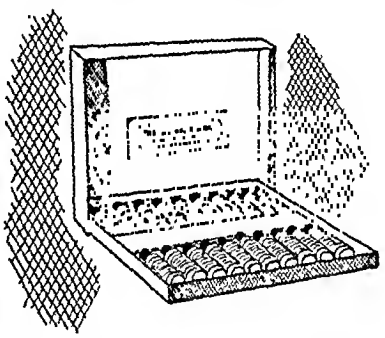

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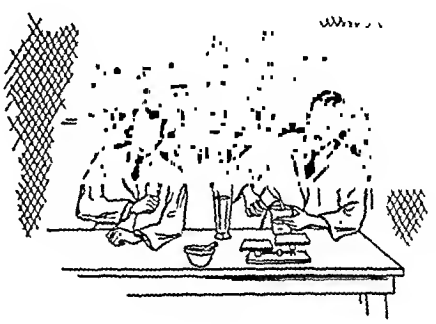

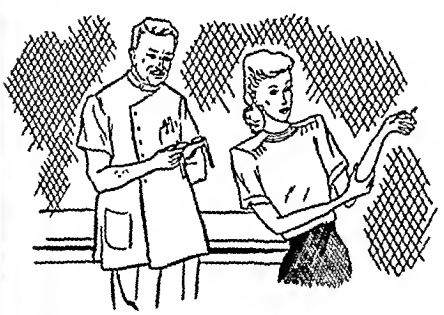

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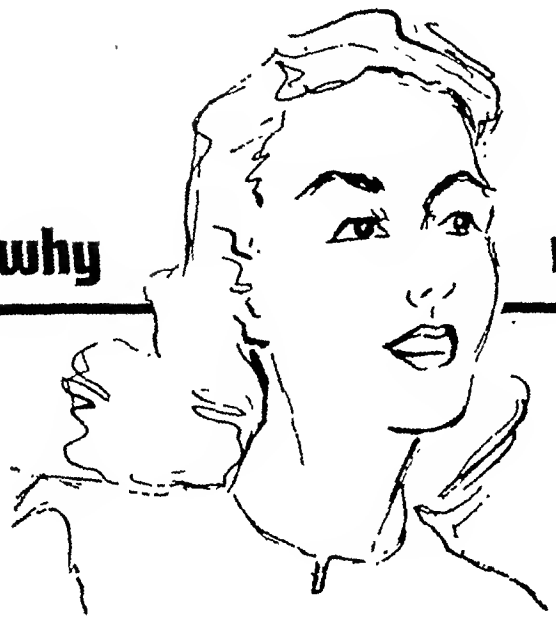

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

X. Intrinsic Fungus Factors in Relation to Asthma

L. O. DUTTON, M.D., F.A.C.A.
El Paso, Texas

PREVIOUSLY I have offered some remarks upon a device used by me to discover certain types of allergic clinical patterns due to fungi. Briefly, this device consists of routine culture of the sputum of asthmatic patients by methods designed to facilitate the growth of fungi and the clinical and immunological evaluation of the significance of the strains isolated.

The technique of the method is simple and brief. In the course of study of the sputum from asthmatic patients, careful attention is paid to the recognizable fungus elements which might be seen on wet mounts and stained preparations. In addition, cultures are done by the spot method on Sabauraud's agar, using 30 to 50 spots to a Petri plate surface. These spots should be inoculated by touching the surface with a loop of sputum but avoiding streaking. If the loop contains a large amount of inoculum it may be touched two to four times to the surface. The loop should be resterilized and a sample selected from a different portion of the specimen, making sure that all portions are sampled which present different gross characters. Adequate sampling is important. The usual bacteriological technique designed to select only the portion of the specimen likely to arise from a pathological lesion and to contain pathogens must be avoided. The object here is to discover the possible presence of fungi from any part of the respiratory tract quite apart from it's pathogenicity in the usual sense. The plates are sealed to prevent drying and incubated at room temperature for two to three weeks. Most positive specimens show recognizable growth within the first week.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

In general, those specimens which yield no more than one or two colonies of fungi are not considered further unless the clinical course suggests a restudy at some later date, as will be detailed below. Specimens which yield growth of fungi in 50 per cent or more of the spot inoculations are earmarked for more complete study. This criterion is only arbitrary as it is apparent that by improper sampling one may obtain either no fungi or 100 per cent growth in the spots from specimens in which the distribution of organisms is scattered.

Only occasionally does one encounter a specimen which yields more than one strain of fungus. Also only on rare occasions have fungi of pathogenic significance been found.

Recently an additional method has been employed to secure samples for culture. This has been the use of nasal swabbings or washings for culture and has been employed too few times to permit evaluation of its usefulness.

Admittedly, by this procedure, one will encounter numerous specimens from which fungi may be isolated which prove to be without significance. It is necessary, therefore, to adopt some criteria by which to select those on which more careful study is to be done. These criteria are:

1. A yield of 50 per cent or more growth in inoculated spots.
2. A repetition of positive findings, although variable in percentage of positive spots, in specimens collected at intervals of several days and repeated with three to six specimens.
3. A yield of any fungi in specimens from patients who have presented no evidence of other more commonly recognizable etiological factors.
4. A yield of fungi variable in percentage of growth from zero to 50 per cent or more, as observed in multiple specimens, the percentage of growth varying in direct proportion to the intensity curve of the patient's symptoms.
5. A yield of growth of any proportion in patients whose x-ray findings suggest the possibility of a primary fungous infection.
6. A yield of growth which on initial study is minimal in proportion but is isolated from a specimen suggesting a bacterial etiology, and which increases to maximal proportions following antibiotic therapy, which fails to improve or even intensifies the clinical symptoms.

To these criteria, of course, must be added the general consideration that more common etiological probabilities should be explored, as usual, by history, skin testing and experimental trial.

After it is decided that consideration must be given to the possible etiological significance of the strain of fungus isolated, the organism is isolated in pure culture, grown to maximal concentration in an acid, high-sugar-content broth. The broth is decanted, filtered and preserved. The mat of fungous growth, without preliminary drying, is extracted with a

saline extracting fluid for forty-eight hours, then is filtered and glycerine is added in equal proportions.

These two products are then used to do skin tests, using sterile broth as a control. Cutaneous tests are done first with the undiluted broth and extract. If negative results are obtained, intracutaneous tests are then done, using ascending strengths, beginning with dilutions of 1:1,000 and increasing to undiluted broth and 1:10 dilution of the glycerinated extract. Controls of similar dilutions of broth and glycerinated extracting fluids are used. If positive reactions are obtained, passive transfer sites are prepared and tested.

If clinical and mycological evidence is suggestive and the skin tests are positive, treatment is then carried out essentially as in pollen therapy. It is not felt that the failure of passive transfer is a contraindication to therapy.

With such extracts it has been possible to produce an exacerbation of symptoms and/or urticarial systemic reactions. Improvement in the clinical picture in a small but significant proportion of patients who had otherwise presented the clinical features of intractable asthma has been obtained.

Clinically these patients may be separated into three fairly definite categories.

First, an occasional patient will present the necessary mycological findings together with x-ray or other evidence of pulmonary fungus disease.

Such a case is that of Mrs. P. This patient, aged forty, had had definite allergic episodes of flexural dermatitis and urticaria previous to the onset of asthma. The asthma had been present for two years at the time of the initial study. During these two years, symptomatic treatment, skin testing, trial dieting and history had failed to indicate the possible etiology or to relieve the patient of her symptoms.

Cultural studies, as outlined above, gave heavy growth of a Monilia type fungus. X-ray studies revealed a patchy, atypical infiltrative reaction considered to be probably of mycological origin.

Skin tests with extracts were considered to be significantly positive. Treatment was instituted by hyposensitization, and marked improvement in asthmatic symptoms was obtained after about three months. However, the productive cough, positive cultures and x-ray findings remained essentially as described. Therapy was then directed to the primary disease, chiefly by repeated courses of iodides and deep x-ray. Gradually the symptoms subsided over a period of three years, and eventually the sputum cultures became negative for Monilia.

Only two other cases essentially similar to this have been seen. In this type of case, one must emphasize the protracted and intensive nature of the therapeutic approach to finally achieve success.

The second fairly definite category into which these patients may be placed is that in which symptoms are fairly constant, cultural findings are likewise constant, and no evidence of infiltrative lesions or other evidence of pulmonary fungus disease exists. One can well postulate that these cases are examples of intrabronchial parasitic but nonpathogenic

fungus infestations to which the patient has become allergic, with resulting asthmatic symptoms.

Such a case is that of Mr. T., aged twenty-four. Five years previous to the initial study he had experienced a protracted "cold which had developed into flu-pneumonia" (this is the patient's description). The nature of this initial illness is, of course, obscure. Following several months of cough, asthmatic wheezing developed which, although paroxysmal, occurred almost daily. The usual history and skin tests failed to reveal significant findings. Cultures produced about 50 per cent spot growth of a fungus which was not identified except that the usual pathogenic types were excluded. Identical findings were obtained on four sputum specimens, studied at intervals of four days. Extracts gave large typical skin reactions by the scratch test. Treatment was strikingly successful. Symptoms subsided rapidly. After two months, no further asthma occurred. Slight cough with minimal production of sputum persisted for six months. Cultures taken at intervals during treatment showed gradual decline in the number of positive spots, and no growth was obtained after the fifth month. The patient was well six years after first seen—five years after treatment was discontinued.

Twenty patients have been seen essentially similar to this. Results have been strikingly good in nine of these, helpful or fair in five, and failures in six.

The third group of patients consists of those in whom symptoms are paroxysmal and the history suggests some environmental factor as the offending one. Cultures show sporadic growth of fungi. Other etiological factors are excluded by test or therapeutic trial.

Such a case is that of Mr. B., aged twenty-six. This patient was the coach of a high school football team which practiced daily on a Bermuda-grass playing field. During his second season on this field, asthma began to occur during the practice session. This was the first recognized allergy in this patient. It seemed obvious that Bermuda sensitivity was the most logical offender in this case. However, scratch and intracutaneous tests to Bermuda pollen were negative. Also the season of pollenation had terminated, and the grass was in a dormant state. Exposure to other Bermuda stands (a golf course ten miles distant from the football field) failed to induce asthma. This puzzle resolved itself after finding a heavy growth of an Alternaria type fungus from the nasal washings obtained shortly after being on the field. Examination revealed a heavy parasitization of the dead Bermuda leaves and stolons by Alternaria. Skin tests with our routine Alternaria extract gave a mild suggestive reaction by intracutaneous test. An extract prepared from the Alternaria strain isolated, however, produced a maximal reaction, by scratch test, 3 inches in average diameter, and an attack of asthma which required control with adrenaline for six hours. Therapy was not attempted in this case. By this time our studies were completed, the football season was over, and the following year the patient changed his work to avoid contact with the offending agent.

Another case of interest in this group is that of Miss Y., aged twenty-two. This patient presented herself with a complaint of seasonal hay fever of summer and fall type, of several years' duration. Symptoms coincided sharply with the grass and weed seasons of her locality, and this was confirmed by satisfactory skin tests, positive reactions being obtained to Bermuda, Russian thistle and Palmer's amaranth. Hyposensitization was instituted coseasonably, with minimal doses in August, and relief of symptoms occurred within two weeks following institution of treatment.

Due to the very long combined grass and weed season in our locality (May to mid-November), perennial treatment was carried out, with gradual increase of dose to near tolerance during the year following the first season. The second season's results were excellent. No asthma occurred and only occasional mild hay fever occurred. Following this season the patient discontinued treatment. The third season, under observation but with no treatment, justified the patient's decision to omit treatment, as no symptoms occurred. This excellent state of affairs continued during the fourth season, until late October when she presented herself again with marked asthmatic symptoms and cough which produced a clear mucoid sputum without pus but with many eosinophiles. This seemed to be such a clear-cut example of return of symptoms following two seasons without treatment that her first pollen mixture was used to immediately institute coseasonal therapy. However, her sputum had been processed routinely, and it was surprising to me when a yield of 80 per cent positive growth of a fungus was found after several days. On maturity this was found to be an Alternaria type strain. It was then recalled that on the first skin testing the patient had given a 4-plus reaction to Alternaria. This fungus had not been included in her initial treatment mixture, however, because of the sharp coincidence of her symptoms with the grass and weed seasons, and the experience that all previous cases of Alternaria clinical sensitivity seen in our locality had presented perennial symptoms with a marked spring (previous to grass season) and late fall peak.

Another sputum specimen was examined by digesting the tenacious mucus with caroid powder and centrifuging. The sediment showed the presence of a moderate number of Alternaria spores but no evidence of mycelial formation. Questioning revealed that the first symptoms of cough and asthma for this recurrence had occurred while the patient had been gathering beans from her family's commercial truck garden. (This had been her occupation throughout the course of our contact with the case.) Some of the leaves from these bean plants were examined and found to be heavily parasitized with Alternaria.

A re-check of the skin test again showed a strong positive scratch test, and passive transfer was definitely positive. These tests were done with a stock Alternaria extract. In this case, extracts were not made from the strain isolated from the patient's sputum.

Treatment of this case consisted of a few minimal doses of Alternaria extract and strict avoidance of the parasitized bean patch. The asthma and cough subsided promptly and treatment was discontinued by the patient's choice. Two years later, when last contacted, the patient continued free of asthma and hay fever.

Another case of interest, but not fitting into any clear-cut group, is that of Mrs. B., aged thirty-six. This patient was first seen four years ago with a long history of asthma which had begun following a respiratory infection of unknown nature. She was extremely underweight and presented the symptoms of a paroxysmal cough which raised copious quantities of purulent sputum. There was paroxysmal dyspnea of nonasthmatic type. X-ray and physical examination indicated a diagnosis of bronchiectasis and bronchitis. There had been many studies, by physicians in many cities, done on this patient with exhaustive skin tests and trial dietary. There had been many periods of hospitalization. She had been placed on morphine, with resulting addiction, and when first seen was taking 3 grams daily. She rebelled at the suggestion of further hospitalization. The outlook for therapeutic success with her was indeed gloomy. Study was undertaken in a half-hearted manner, both on my part and on the part of the patient. Routine studies on the sputum revealed eosinophilic and cosmophilic cytolyses with a predominating bacterial growth of [illegible] hemolytic streptococci. Sabouraud's plates showed [illegible] of Mold a

For a year, therapeutic attempts consisted of efforts to minimize the inflammatory process by the usual means—all of which had been attempted before. She continued to present all of her symptoms and continued in the use of narcotics. Repeat sputum cultures continued to reveal the same findings as outlined above, with no variation in the Monilia contents.

At this juncture we first began the use of penicillin by the aerosol method. The patient was persuaded to submit herself to a trial of this and was forced into the hospital by the refusal to furnish further narcotics. The aerosol was begun with the use of 20,000 units of penicillin given five times daily. Within four days there was a marked reduction of the amount of sputum and a change in its character from purulent to mucoid. However, the cough continued to be troublesome, but no asthmatic wheezing was heard. As withdrawal of narcotics was being attempted and the patient was extremely wilful and headstrong, the cough was discounted—especially as the physical findings had improved: the low grade fever had subsided, and there had been a significant gain in weight. After six weeks of hospitalization, narcotics had been successfully withdrawn and there had been a marked improvement in all aspects of the case, except the continued cough (much less intense) and mucoid sputum. The aerosol had been gradually reduced in frequency, and the final week only two inhalations had been given. Re-study of the sputum at this juncture showed an almost total absence of coccoid flora. No replacement by B. coli or other bacterium was found. However, the microscopic and cultural findings indicated a passive population of a Monilia-type fungus. Skin test with stock Monilia extracts was positive—both immediate and delayed—by the intracutaneous technique. Passive transfer was negative. Before autogenous extracts could be prepared, the patient was dismissed from the hospital. She made a trip to another city, and her stay proved to be permanent. Through acquaintances it was learned that after several months she began to decline and was again under medical care.

DISCUSSION

We believe that the methods outlined above offer valuable aid in the management of a selected, though significant, group of intractable asthmatic patients. Admittedly there are many deficiencies in these studies. Passive transfer has been attempted in only one-fourth of the cases seen. It has been positive, however, in six of the eight attempts. Many cases have been encountered giving a few colonies of fungi which have not been studied more completely to evaluate their significance. No attempt has been made to evaluate these findings statistically. As I have previously said, from the patient's viewpoint his own problem constitutes 100 per cent of his interest. Nor has any attempt been made to identify beyond simple type grouping the strains of fungi encountered. As this work has all been done in private practice, those familiar with the difficulties of mycological study can readily appreciate the reason for that omission.

From my experience, which has extended over sixteen years with this type of study, I feel convinced that several reliable conclusions can be drawn. First, it seems apparent that the source of fungus exposure may reside within the respiratory passage without there being recognizable infiltrative pathologic conditions associated with them. Under such conditions it also seems possible for these fungi to behave as to other allergens.

The use of this type of study will occasionally detect a fungus spore

etiology in patients exposed to an otherwise unsuspected heavy concentration of fungi.

In one case detailed above, only small questionable skin reactions were obtained with stock extracts, while maximal reactions and systemic reactions were obtained with autogenous extracts. This may be due to one of several possibilities. Identical species of fungi may vary widely in antigenicity from strain to strain. Or closely related species which do not present identifiable features on superficial study may exist and give some cross reaction due to antigenic similarity or to the presence of multiple antigens of varying nature. A third possibility is that the method of extracting fungi outlined above yields products of much more antigenic potency than those obtained by the widely practiced method of drying and washing fungous growth before extracting. One must admit, of course, that extracts prepared as outlined above would be impossible to duplicate and difficult to standardize. On the other hand, fungi which are dried and washed, defatted and otherwise treated before extraction are probably denatured in an undetermined degree. We have additional evidence to suggest that this latter statement is probably correct. It also seems apparent from the last case detailed above, plus two additional cases not here reported but of similar findings, that effective antibiotic aerosol therapy may permit the abundant overgrowth of a fungus present in only minimal amount previous to treatment. The significance of this has not been evaluated but is now under study.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XI. Phytopathogenic Fungi in Aerobiological Populations

MARIE BETZNER MORROW, PH.D., and HARRY DELBERT THIERS, M.A.
Austin, Texas

THE SUBJECT of fungi in relation to inhalant respiratory allergy has become recognized by physicians, mycologists, plant pathologists and others whose interests extend into this field. It has been definitely established that many of these fungi are carried in the air from infected plants in the case of phytopathogens and from their several sources in the case of saprophytic forms. The relatively small number of reports on phytopathogens may be due in part to the fact that in many of the surveys which have been conducted, the agar plate method was used; consequently, the obligate parasites were missed. It is probable also that in many studies where the slide method was employed, spores of phytopathogens were overlooked. Interested workers cannot but recognize that many problems are open for investigation. Much information is needed on the fungi in the role of allergens. But before this phase of the problem, which is a clinical one, can be studied adequately, more information is required concerning the fungi themselves. This is particularly true of the fungi which cause plant disease. It would simplify matters, indeed, if, when a source of infected plant material is located in a given environment, it could with some certainty be identified as a potential source of allergenic material in the air population in that locality, or as surely be ruled out. It seemed desirable, therefore, to conduct a series of studies in this laboratory which would contribute to the particular problem of phytopathogens and their possible role as allergens.

The studies were planned for the purpose of finding out what relations exist between fungus-infected host plants in a given location and the air population at that location, and at near and farther distances from the host symptoms within an area of approximated limits or outposts. One objective was to determine if host symptoms of a particular plant disease in a given location are an index to air-borne spores of that particular pathogen; that is, if fungus-diseased plants are located, does it follow that spores of the pathogen are carried aloft and will be encountered in the air population at this location? Specifically, can one expect to find Dichondra rust spores on slides exposed in this vicinity, if rust-infected Dichondra turf is located? In other words, might Dichondra turf indicate a possible source of allergenic material in cases of inhalant respiratory allergic diseases?

A second objective was to determine whether those spores which are

From The University of Texas, Austin, Texas.
Dr. Morrow is an Honorary Fellow of The American College of Allergists.
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known to be carried aloft at the host infection site are also carried away from the infection sites, and if possible, to what distances, that is. within the outposts. Specifically, if the spores of the powdery mildews are carried aloft and are encountered in the air population at the infection site, might they be expected also to be recovered as air constituents ten city blocks distant from the host symptoms? In other words, might the spores of powdery mildew on crape myrtle on the University campus be expected to be encountered on slides exposed on San Antonio Street, and thereby constitute a potential source of allergenic material for residents there who do not frequent the campus?

A third objective was to determine whether spore incidence in the air is seasonal, and if so, if it corresponds with the seasonal aspects of host infection. Specifically, are there peaks for spore concentration of plant pathogens as air constituents, and if so, do these peaks correlate in any way with the intensity of the host symptoms? In other words, is there a Bermuda grass smut "season" or a Johnson grass smut "season," and might one expect to find Johnson grass smut in the air in December after frost has killed the hosts? The answers to any one or all of these would be specific, yes, or no, but would have to be determined individually for each phytopathogen under investigation.

The Austin region provides hosts for at least three well-known and economically significant plant diseases, namely, rusts, smuts, and powdery mildews. These include those pathogens most commonly referred to in the literature of aerobiology, the smuts and rusts, as well as those mentioned infrequently or not at all, the powdery mildews.

For the purpose of the studies, smuts of Johnson grass and Bermuda grass, rusts of Johnson grass and Dichondra, and powdery mildews of crape myrtle, Evonymus and wild China were selected and designated as "selected pathogens."

1. Johnson grass smut, *Sphacelotheca sorghi* () Clinton on Johnson grass, *Sorghum halepense* () Pers. ("covered kernel smut").
2. Bermuda grass smut, *Ustilago cynodontis* P. Henn on Bermuda grass, *Cynodon dactylon* () Pers. ("covered smut")
3. Johnson grass rust, *Puccinia purpurea* Cooke on Johnson grass, *Sorghum halepense* () Pers.
4. *Dichondra* rust, *Puccinia dichondrae* Mont. on *Dichondra caroliniensis* Michx.
5. Powdery mildew, *Uncinula australiana* McAlpine on crape myrtle, *Lagerstroemia indica* L.
6. Powdery mildew, *Microsphaera alni* Wallr. on *Evonymus* sp.
7. Powdery mildew, *Uncinula circinata* Cke and Peck on wild China, *Sapindus drummondii* H. and A.

Johnson grass smut, Dichondra rust, powdery mildew on crape myrtle and on Evonymus appear more or less simultaneously in early April; Bermuda grass smut appears in early June, powdery mildew on wild China the first week in July, and Johnson grass rust sometimes later in July. In the

case of the smuts and rusts, superficial symptoms of infection are diminished to the point that the host plants appear normal following mid-July, but symptoms reappear in the fall. The powdery mildews do not show this seasonal variation.

Characteristic spore types (including chlamydospores in the smuts, urediospores in Johnson grass rust, teliospores in Dichondra rust, and conidiospores in the powdery mildews) have their own identifying features and can be recognized with certainty. This holds for the conidiospores of the different powdery mildews.

Locations or areas of infected hosts were designated as "infection sites." "Respective sites" and "corresponding sites" were used for specific pathogens. The sites chosen were located on or near the campus of The University of Texas and are representative of infection areas in the Austin vicinity. These are included in an area comprising some twenty-five to thirty blocks which pass through a portion of the campus from one residence section to another.

Site 1. Smut-infected Johnson grass. Home Economics Building, north, east.
Site 2. Turf of Bermuda grass, smut-infected. Chemistry Building, north.
Site 3. Rust-infected Johnson grass. Waller Creek, east.
Site 4. Carpet of Dichondra, rust-infected. Hogg Memorial Auditorium, west.
Site 5. Powdery mildew-infected crape myrtle shrubs. Union Building, north; Hogg Memorial Auditorium, west.
Site 6. Evonymus hedge, powdery mildew-infected. Residence, 24th and San Antonio Streets.
Site 7. Powdery mildew-infected wild China tree. Union Building, east.

Samples of the air population were obtained on adhesive slides at "sampling sites" or "exposure sites." These were selected within 20 to 30 feet of heavily infected host plants for each of the pathogens, at levels representative of the air content with which sensitive individuals come in contact.

The period of investigation extended from April 2 to July 17, 1946. Slides were exposed daily in duplicate and allowed to remain in place for twenty-four hours. Supplementary surveys were made the following December and again in January.

The present paper is a separate and distinct one from a longer dissertation on phytopathogenic fungi in aerobiological populations, which is in manuscript, to be published soon in detailed form. Some of the facts and figures revealed in the studies, however, lend themselves to a short paper, and are presented in summary form, where, relieved of cumbersome details, results can be discussed to the point. Details of method, qualitative and quantitative tables and lists, figures, graphs, photographs, and other details, while invaluable for the record, are omitted here, as well as historic aspects, but all of these will have their place in the longer work, which will be a companion piece to the shorter paper. For the task of collecting a voluminous amount of data, special credit is due the junior author.

As indicated by their presence on slides exposed at the corresponding sampling sites, spores of six of the pathogens, the smuts, Johnson grass rust, and the powdery mildews are air-disseminated and apparently constitute a considerable fraction of the air population at the respective infection sites. These therefore would come into the "potential" category with respect to allergenic significance in inhalant respiratory diseases. Dichondra rust presents a unique and different picture. Spores were never encountered on any of the exposure slides, not even when the slides were placed under the infected plants. It would seem that these are not air-disseminated, and the plants therefore would be eliminated from the probability of allergenic significance.

Recovery of spores at the corresponding sampling sites would imply that these are carried short distances from the infected hosts in each case, at least the 20 or 30 feet representing the distance from infected plant to exposure site. This would seem to lend support for these in the potential category with respect to their allergenic significance.

Recovered only at the corresponding sampling sites, spores of Bermuda grass smut, Johnson grass rust, and the Evonymus and wild China powdery mildews are apparently limited to the immediate vicinity of the infected plants, and consequently have potential allergenic significance only in a local environment.

As indicated by recovery of spores at the various other sampling sites, which involved their being carried considerable distances in some cases, Johnson grass smut and crape myrtle powdery mildew would seem to have a more extensive range of dissemination, and consequently would have potential allergenic significance in wider environments.

Seasonal variation is strongly indicated for the smuts, less so for the rusts, and little or not at all for the powdery mildews. A continuing increase in spore numbers in the air generally followed an increase in host infection, whereas a decrease was noted when growth of the host was curtailed by unfavorable weather. In the case of Johnson grass smut, spores were recovered from the air after host symptoms had disappeared in the fall and winter. It would seem, then, that even after host symptoms are no longer present in a given environment for some phytopathogens, spores may continue to be present in the air and constitute a potential hazard for sensitive individuals.

Each plant disease poses its own problems. It has been shown that although in six of seven cases host symptoms indicate air-disseminated spores, there is the exception in Dichondra rust. Likewise, although spores are no longer encountered in the air after host symptoms have disappeared in five of six pathogens, there is the exception in Johnson grass smut.

The postseason aspect of Johnson grass smut as a component in the air population cannot be overlooked as having possible clinical significance.

Other points revealed by these studies appear in the long paper, the other air constituents encountered on the exposure slides being one of

these; numbers of the air components is another; whether the spores occur singly, in masses, chains, or other grouping, is another. The studies have been very revealing, and a considerable amount of data has been assembled.

Results of the studies, as indicated and discussed in this paper, have, however, added certain information in the nature of answers, at least in part, to the questions raised as objectives at the beginning of the investigation. First, spores of plant disease fungi do get into the air population by air dissemination; that is, spores of some phytopathogens are air disseminated. But since at least one of these is not, it can only be said that host symptoms are but potential sources of air-borne spores, which in turn may or may not have allergenic significance, and the diseased plants are therefore only potential hazards with respect to inhalant respiratory disease, but, as such, would of necessity have to be investigated in analyzing an environment.

Secondly, spores that are air disseminated may be carried distances near or far from the diseased plants. In the cases of some of these, the spores are confined to the air population near infected hosts; in other cases, the spores seem to be widely disseminated, and are found at greater distances from the plant hosts. Infected plants that constitute potential hazards in inhalant respiratory disease, then, fall into two groups: those that are concerned with local environments, and those having significance in wider environments.

Thirdly, for some air-borne phytopathogens, there is a "season," but for others, this is not indicated. For some, seasonal aspects are a reflection of host symptoms. For others, there is a "postseason" for the spores of the fungus after host disease symptoms have disappeared.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XII. Further Studies with Mold Extracts

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PREVIOUS studies by the Association of Allergists for Mycological Investigations[1] have indicated the superiority of an acetone-precipitated extract of *Alternaria tenuis* over antigens prepared by various other conventional and experimental methods. The work which forms the basis of this report was undertaken for the purpose of evaluating further this method of extraction, not only for Alternaria but for other commonly encountered molds of the dematiaceous group as well.

It might be recalled here that some of our earlier experimental extracts[3] were made from *Aspergillus niger* as well as from *Alternaria tenuis.* Eventually, however, after it was discovered that definitely positive reactions were not obtained frequently with *Aspergillus niger,* this species was abandoned for further studies in favor of *Alternaria tenuis,* which has a relatively high sensitization index. For like considerations, it occurred to us that since reactions to other dematiaceous molds are encountered with some regularity and often also when Alternaria reacts, a study of related molds would seem most logical. Also, if the technique should prove adequate for these other molds, not only would the merits of the method be enhanced, but some practical indication regarding criteria for evaluating multiple reactions in this group might be noted.

Accordingly, in the summer of 1947 glycero-saline extracts were prepared by our experimental Technique 33 (acetone precipitation) from *Hormodendrum cladosporioides, Helminthosporium interseminatum,* a Spondylocladium species, *Curvularia trifolii* and *Nigrospora sphaerica,* as well as from *Alternaria tenuis.* At the same time the nonprecipitated discard products resulting from the preparation of four of these extracts (Alternaria, Hormodendrum, Helminthosporium and Spondylocladium) were concentrated by evaporation and were prepared into extracts comparable qualitatively with the extracts of the acetone-precipitated fraction. All extractions were carried out simultaneously so as to minimize differences due to aging. The finished products were distributed to our collaborators for testing and neutralization experiments.

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TABLE I. DIRECT AND INDIRECT SKIN SENSITIVITY TESTS

Mold	Patch	Direct Tests: Intradermal 1:100,000	1:10,000	1:1000	After [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Patient 5 (Bastian)																
Alternaria	+ + +		+ + +		+ + + +		+ + + +	+ +		+ + +	+ + +		+ +	+ +	+ +	+ +
Hormodendrum	+		+		+ + + +		+			+ +				+		
Helminthosporium	+		+		+ + + +		+			+ +				+	+	
Spondylocladium	+		+		+ + + +		+			+ +		+		+ +		
Curvularia	+ +		+		+ + + +		+ +									
Nigrospora	+															
Control																
Patient 6 (Hicks)																
Alternaria	+	+ + +			+ + + +		+	+ +			+		+ +	+ +	+ +	+ +
Hormodendrum	+		+		+ + + +		+ + +									
Helminthosporium	+		+		+ + + +		+ + +							+		
Spondylocladium	+		+		+ + + +		+ + +								+	
Curvularia	+		+		+ + + +		+ + +			+						
Nigrospora	+															
Control																
Patient 7 (Crawford)																
Alternaria	+			+ + +	+ + + +					+ +	+ +	+	+ +	+ +	+ +	+ +
Hormodendrum	+			+ + +	+ + + +					+ +						
Helminthosporium	+			+ + +	+ + + +					+ +				+ +		
Spondylocladium	+			+ + +	+ + + +					+ +	+		+ +		+	
Curvularia	+			+ + +	+ + + +					+ +						
Nigrospora	+				+ + + +											
Control			+													
Patient 8 (Gordon)																
Alternaria	+		+ + +	+	+ + + +	+	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Hormodendrum	+		+		+ + + +		+ + + +	+	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Helminthosporium	+		+ + +		+ + + +	+ +	+ + + +	+	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Spondylocladium	+ + +		+ + +		+ + + +	+	+ + + +	+	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Curvularia	+		+		+ + + +	+	+ + + +	+	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Nigrospora	+															
Control																

(1) Two retests with Hormodendrum necessary to neutralize
(2) Two retests with Helminthosporium necessary to neutralize

TABLE I. DIRECT AND IN VIVO NEUTRALIZATION TESTS

Mold	Direct Tests				Neutralization Tests											
	Punch	Intradermal			Alternaria	Retest	Hormodendrum	Retest	Helminthosporium	Retest	Spondylocladium	Retest	Curvularia	Retest	Nigrospora	Retest
		1/100,000	1/10,000	1/1,000												
Patient 13 (Duffy)																
Alternaria			++++		++++	−	++++	+++	+++	++++	+++	++++	+++	++++	−	++++
			+		+									+		+
Hormodendrum			+++		+++	−	+++	−	+++	−	+++	−	+++	++	−	+++
			+		+											
Helminthosporium			++++		++++	−	++	−	+++	−	++	−	++	+	−	++++
			++		+											
Spondylocladium			++++		++++	−	+++	−	++	−	−	−	−	+++	−	+++
			++		+											
Curvularia			++++		++++	−	++	−	+++	−	++	+++	−	−	−	++++
					+											
Nigrospora			++++		++++	−	++	−	+++	−	++	−	−	−	−	−
					+											
Control																
C.E.A. Recipient 1 Serum diluted 1:5 Homologous test injections were made into each site three times before cross testing. All six neutralizations were made simultaneously.																
Patient 13 (Duffy)																
Alternaria			++++		++++	−	++++	++++	+++	++	++++	++++	+++	++++	−	++++
			+		+			+						+		+
Hormodendrum			++++		++++	−	++++	−	+	−	+++	−	++++	++	−	++
			+		+											
Helminthosporium			++++		++++	−	+++	++	+	−	−	−	−	+	−	++
			++		+											
Spondylocladium			++++		++++	−	+++	++	+	−	−	−	−	−	−	+++
			++		+											
Curvularia			++++		++++	−	++	+	++	−	++++	+	+++	−	−	+
					+											
Nigrospora			++++		++++	−	++	−	++	−	−	−	++	−	−	−
					+											
Control																
C.E.A. Recipient 2. Serum diluted 1:5. Homologous test injections were made into each site three times before cross testing. All six neutralizations were made simultaneously.																
Patient 14 (Hedley)																
Alternaria			+++		++++	−	+	++++	−	++++	−	++++	−	++++	−	++++
Hormodendrum			+++		++++	−	++	−	+	++	−	+	−	++	−	−
Helminthosporium			++		++++	−	+++	−	+	−	−	−	−	−	−	−
Spondylocladium			−		++++	−	++	−	+	−	−	−	−	−	−	−
Curvularia			−		++++	−	++	−	+	−	−	−	−	−	−	−
Nigrospora			+		++++	−	−	−	−	−	−	−	−	−	−	−
Control					++++		++		−		−		−		−	
C.E.A. Serum diluted 1:5. Homologous test injections were made into each site three times before cross testing.																

IMMUNOLOGICAL STUDIES

Patients were selected who were thought to be clinically sensitive to Alternaria or other dematiaceous molds; in most instances several or all of these molds elicited positive reactions (Table I). Patients thus selected were retested with the experimental molds and discard products both by the scratch or punch method and by the intradermal technique. Sera from some of these patients were sterilized by Seitz filtration and preserved by the addition of one-hundredth volume of aqueous merthiolate 1:100, making a final concentration of 1:10,000 merthiolate.

A. In-Vivo Neutralization Studies.—Into each of six sites in a vertical row on the left aspect of the recipient's back was injected 0.08 to 0.10 c.c. of serum, and the places marked with indelible ink. A similar site to serve as a control was prepared either above the others or on the lateral aspect of the upper arm. Two days later each site was tested with 0.05 c.c. of Alternaria 1:1,000; a control test was also made in normal skin. After another twenty-four hours the first site was again tested with Alternaria, and if all reagin had been exhausted by the first test, indicated by a negative reaction, the remaining sites were tested in order with the other five molds. The control site higher on the back or on the arm was then tested with Alternaria to verify the persistence of reagin. In one or two instances retest of all the sites with the homologous mold was necessary to effect complete neutralization before proceeding with the cross testing after an additional twenty-four hours. After completion of the tests another row of sites was prepared to the right of the first for similar exhaustion by Hormodendrum. In like manner each of the molds in turn was studied (Table I). All tests both for the initial exhaustions as well as for the cross reactions were accompanied by control tests in normal skin, according to the Prausnitz-Kustner technique.

B. In-Vitro Neutralization.—The neutralizing mixtures of allergen and sensitive serum were prepared by placing 0.30 c.c. each of 1:1,000 mold extract, serum, and normal saline into sterile test tubes which, after thorough shaking, were allowed to stand in the refrigerator over night. Into each of six sites arranged in a vertical row on the left side of the recipient's back was injected intradermally 0.10 c.c. of this mixture. At the same time control sites A and B were prepared on the outer aspect of the upper arm as follows: Into site A was injected 0.10 c.c. of a 1:3 dilution of serum in normal saline (the serum in control A therefore was in the same dilution as in the serum-antigen-saline mixtures). Into site B was injected 0.10 c.c. of undiluted serum. After forty-eight hours the sites on the back were tested with 0.05 c.c. of each of the respective mold extracts 1:10,000, and the control sites A and B were tested with the homologous mold. Within a few minutes if no reactions occurred, or after five or

six hours to allow reactions to subside, the sites were again tested with the same molds in 1:1,000 dilution. In like manner neutralization with each of the molds in succession was performed. The results are recorded in Table II. In both the *in-vivo* and *in-vitro* experiments, some variations were made from the technique as given above; such modifications are noted in the tables.

RESULTS

At the outset we wish to stress the fact that these studies, involving several mold-sensitive allergic patients, can only be expected to reveal differences in sensitization to the various molds depending on the reaginic activity of the individual patients and their sera. Therefore, any conclusions must be interpreted with this in mind and cannot be construed as confirming otherwise defined botanical relationships between the molds themselves.

In most of the sera studied in experiments A and B, Alternaria exhausted the reagins for all other molds. However, Alternaria failed to exhaust reagins for Helminthosporium and Spondylocladium in the *in-vivo* neutralization, and for Helminthosporium in the *in-vitro* experiment with serum 1; for Helminthosporium and Curvularia in both experiments with serum 3, and for Spondylocladium in the *in-vivo* studies with sera 8 and 9. Conversely, in serum 1, Spondylocladium, Curvularia and Helminthosporium appreciably diminished, but did not entirely block the reaction on cross testing with Alternaria in both experiments. In serum 3 Curvularia completely exhausted reagins for Alternaria, while Helminthosporium and Spondylocladium greatly diminished the reaction in the *in-vivo* experiment; all three apparently diminished the reaction on cross testing with Alternaria in the *in-vitro* study. In sera 8 and 9 furthermore, Spondylocladium exhausted reagins for all molds except Alternaria, whereas no Heterologous mold including Alternaria exhausted reagins against Spondylocladium. In all the tests Hormodendrum neutralized Nigrospora reagins, but the reverse was not true in five instances.

In general, the antibody exhausting power of any particular mold seemed unpredictable, except for the fact that those molds giving large transfer reactions on the initial testing in the *in-vivo* neutralizations seemed to neutralize more reagins for other molds, and they in turn seemed more difficult to be neutralized. Significant differences in reactivity seemed to depend more on the reaginic variations of the sera than on the mold extracts. All the sera varied in reagin content. Serum 10 was exceptional in that it contained reagins to only one mold of the dematiaceous group (Alternaria). In several of the sera reagins were lacking or of low titer for one or more molds. In most instances reagins were present for all the molds.

It is obvious that the *in-vivo* and *in-vitro* tests gave comparable results. Actually, the *in-vitro* procedure is simpler and probably is subject to less error than is the *in-vivo* technique because in the test tube, mixture of

TABLE II. IN-VITRO NEUTRALIZATION TESTS

Serum—Saline—Antigen:	Alternaria		Hormodendrum		Helminthosporium		Spondylocladium		Curvularia		Nigrospora	
Cross testing with:	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/1,000	1/10,000	1/ 1,000	1/10,000	1/1,000
Patient 4 (Hornbuckle)												
Alternaria	−	−	++++	−	+++	−	+++	−	+	−	++	−
Hormodendrum	−	−	−	−	+	−	+	−	−	−	−	+
Helminthosporium	−	−	++	−	−	−	−	−	−	−	+	−
Spondylocladium	−	−	+	−	++	+	−	−	−	−	+	−
Curvularia	−	−	+	−	++	++	++	−	−	−	−	−
Nigrospora	−	−	−	−	++	+++	++	−	++	−	−	−
Control A 1/3 serum	++		+	++	++	−	−	−	−	−	+	
Control B serum undiluted	+++		+	++	++	−	++	−	++	−	++	
Patient 13 (Duffy)												
Alternaria		−		+++		+++		+++		+++		+++
Hormodendrum		−		−		−		−		−		−
Helminthosporium		−		−		−		−		−		−
Spondylocladium		−		−		−		−		−		−
Curvularia		−		−		−		−		−		−
Nigrospora		−		−		−		−		−		−
Control A 1/3 serum												
Control B serum undiluted												

C.E.A.
Neutralizing mixtures: 0.5 cc serum 1:2, 0.5 cc saline, 0.5 cc 1/1,000 mold extracts. All sites tested with homologous antigens and found negative before cross testing.

TABLE III. TESTS WITH EXPERIMENTAL EXTRACTS AND DISCARD PRODUCTS

Mold	Patient 1 (Davies)		Patient 2 (Rowles)				Patient 3 (Keene)		Patient 4 (Hornbuckle)		Patient 5 (Bastian)		Patient 6 (Hicks)	
	Punch	Intradermal 1/1,000	Punch	Intradermal 1/100,000	Intradermal 1/10,000	Intradermal 1/1,000	Punch	Intradermal 1/10,000	Punch	Intradermal 1/10,000	Punch	Intradermal 1/10,000	Punch	Intradermal 1/10,000
Alternaria	+	++++	+	++	+++		++	++	++	+++	+++	+++	++	++++
Discard	+	−	−	−	+		−	+	−	−	−	+	−	−
Hormodendrum	+	++++	+	+	+++		++	+	−	−	+	++	−	+
Discard	−	−	−	−	−		+	−	−	−	−	−	+	−
Helminthosporium	+	+++	−	+	++		++	++	+++	++	+	+	+	+
Discard	−	+	−	−	−		−	+	−	−	−	+	−	+
Spondylocladium	++	++++	+	+	++		+++	++++	++	+	−	−	−	−
Discard	−	−	−	−	−		+	++	−	+	+	+	−	−
Curvularia	++	++++	++	+	++	+	+	+	−	−	+	++	−	+
Nigrospora	−	−	−	−	−		+	+	−	−	++	−	−	+

Mold	Patient 7 (Crawford)		Patient 8 (Gordon)		Patient 9 (Bruggeman)			Patient 10 (Hansen)		Patient 11 (McMinn)		Patient 12 (Hixon)	
	Punch	Intradermal 1/1,000	Punch	Intradermal 1/10,000	Punch	Intradermal 1/100,000	Intradermal 1/10,000	Punch	Intradermal 1/1,000	Punch	Intradermal 1/1,000	Punch	Intradermal 1/10,000
Alternaria	+	+++	+	+++	++++	+	++++	+	+++	+	++	++++	+++
Discard	−	+	−	−	+	−	++	−	+	−	+	+	+
Hormodendrum	+	−	−	+	++	+++	+++	−	−	−	−	−	+
Discard	−	−	−	−	−	−	+	−	−	−	−	−	+
Helminthosporium	+	++	−	++	+	−	++	−	−	−	++	−	−
Discard	−	−	−	−	−	−	−	−	−	+	+	−	−
Spondylocladium	−	++	++	+++	++++	++	++++	−	−	+	++	−	−
Discard	−	−	−	+	++	+	++	−	−	−	+	−	+
Curvularia	−	−	−	++	+++	+	++++	−	−	−	+	−	−
Nigrospora	−	−	+	+	−	−	+	−	−	−	−	−	−

TABLE III. TESTS WITH EXPERIMENTAL EXTRACTS AND DISCARD PRODUCTS

Mold	Patient 13 (Duffy)	Patient 14 (Hedley)	Patient 15 ("III")	Patient 16 (Gordon)		Patient 17 (Franchot)		Patient 18 (Petty)	
	Intradermal	Intradermal	Intradermal	Punch	Intradermal	Punch	Intradermal	Punch	Intradermal
	1/10,000	1/10,000	1/1,000		1/1,000		1/10,000		1/1,000
Alternaria	+++++	+++	++	+	++	++	+++	−	++
Discard	+++	++	+	−	+	−	−	−	−
Hormodendrum	+++++	+++	+++	−	+	++	++++	−	+
Discard	+++	+++	−	−	−	−	−	−	−
Helminthosporium	+++++	++	+++	−	−	+	++	+	+
Discard	+++	−	−	−	−	−	−	−	−
Spondylocladium	++++++	−	+++	−	−	++	++	+	+
Discard	++++	+++	+	−	−	−	+	+	−
Curvularia	++++	−	−	−	−	++++	++	−	+++
Nigrospora	++++	+	−	−	+	−	+	−	+

Mold	Patient 19 (Anderson)		Patient 20 (J.T.W.)			Patient 21 (Darr)		Patient 22 (Stromberg)	Patient 23 (Randel)	
	Punch	Intradermal	Intradermal			Punch	Intradermal	Intradermal	Punch	Intradermal
		1/10,000	1/100,000	1/10,000	1/1,000		1/1,000	1/10,000		1/1,000
Alternaria	++++	+++	++++			−	+	+++++	+	++++
Discard	−	−	−	−	−	−	−	−	−	+
Hormodendrum	−	+	++			+	+++	+++	−	−
Discard	−	−	−	+		−	−	−	−	−
Helminthosporium	++	+	++			+	+++	++	−	++
Discard	−	−	−	−	−	−	−	+++	−	−
Spondylocladium	+	−	+++			+	+++	+	−	++
Discard	−	−	−	−	−	−	−	+	−	+
Curvularia	+	−	++			−	+	−	−	+
Nigrospora	−	−	−	−	−	−	−	−	−	−

antigen and antibody should be more thorough and complete. Unfortunately, we were unable to perform *in-vitro* neutralization on all the sera studied.

SKIN TESTS WITH EXTRACTS AND DISCARD PRODUCTS

The mold extracts and discard products were used in concentrated strength (1:50) for punch (scratch) testing, and in dilutions ranging from 1:100,000 to 1:1,000 intradermally. The tests were made either with arbitrary dilutions intradermally (C.E.A., E.D.S.) or by both the punch (scratch) and intradermal techniques, with the solutions for the intradermal tests being selected on the basis of the preliminary punch (scratch) reactions (P.T.P., H.E.P.). The results of these tests are shown in Table III.

Obviously the discard products contain appreciable amounts of antigen, indicating that not all the skin reactive fractions were retained in the extracts (Patients 13 and 14). However, most tests indicated that the discard products contained relatively much less antigen than the extracts. This is not clearly apparent in Patients 13 and 14 with the 1:10,000 intradermal tests; these patients obviously were very highly sensitive to dematiaceous molds, and probably dilutions greater than 1:10,000 would be required to show differences.

One of us (E.A.B.) injected intradermally 0.10 c.c. of 1:1,000 experimental Alternaria extract into an individual known to be Alternaria sensitive. In three minutes he was wheezing and his nasal passages were blocked in spite of a tourniquet applied as soon as the reaction was detected. Three days later the forearm tested still showed a reaction, the swollen area measuring 1.5 inches, the surface of the arm from the wrist to the elbow being indurated. The discard product of Alternaria, 0.10 c.c. of 1:1,000, gave a negative skin reaction.

DISCUSSION

These experiments suggest that extracts of molds of the dematiaceous group prepared by Technique 33 possess specific allergenic properties. We believe furthermore that the technique is adequate with the other molds of the group as has been pointed out previously for Alternaria. We know that some allergen is lost in the process, but we feel very definitely that this is more than compensated by the increased potency and specificity of the extracts.

In unpublished experiments several years ago, one of us (H.E.P.) was able to neutralize reagins to other dematiaceous molds with Alternaria by the exhaustion of passively sensitized sites, using, however, extracts prepared by our old routine technique.[2] Furthermore, diagnostic and therapeutic results were no better with a mixture of all the dematiaceous molds than with Alternaria alone. Following these observations, reactions with any of the dematiaceous molds were regarded more from the standpoint of substantiating the group sensitization, as typified by Alternaria, than

of indicating sensitization to the particular reacting molds. This interpretation doubtless was influenced further by the fact that Alternaria usually reacted when *any* dematiaceous species did; failure of Alternaria to react often cast doubt on the reliability of the positive tests from others of the group. The use of Alternaria as a *group antigen* therapeutically, therefore, seemed justified.

In the light of the findings presented herewith, the rationale of using Alternaria therapeutically for all reactions to molds of the dematiaceous group must be questioned. It cannot be doubted that Alternaria would probably protect eleven of the fifteen patients reported in Experiment A, but Alternaria alone would be inadequate in Patients 1, 3, 8 and 9 upon clinical exposure to those molds not neutralized. This failure at protection with Alternaria was observed in Patient 1, whereupon re-evaluation of skin test results led to a study of her serum in Experiments A and B.

CONCLUSION

The dematiaceous molds herein studied seem to contain group antigens as well as generic or possibly species antigens. Sensitization to these molds, however, must be evaluated in the light of the actual reagins demonstrable in any given patient; such reagin distribution is variable. Ordinarily it would seem that Alternaria should protect against other molds of the group, but occasionally other molds may assume dominant importance immunologically. If generic or species reagins exist to these other molds, they would require consideration from a therapeutic standpoint.

We hope that with the adequate extracts now available further immunological studies may be made to verify or revise our conclusions, which at this time seem justified.

REFERENCES

1. Prince, Homer E.; Epstein, Stephan; Figley, Karl D.; Wittich, Fred W; Henry, L. Dell, and Morrow, Marie B.; Mold fungi in the etiology of respiratory allergic diseases. IX. Further studies with mold extracts. Ann. Allergy, 7:301-305, 1949.

2. Prince, H. E., and Morrow, M. B.: Mold fungi in the etiology of respiratory allergic diseases. III. Immunologlical studies with mold extracts. I. Preparation of experimental extracts. Ann. Allergy, 2:483, 1944.

3. Prince, H. E.; Tatge, E. G., and Morrow, M. B.: Mold fungi in the etiology of respiratory allergic diseases. V. Further studies with mold extracts. Ann. Allergy, 5:434, 1947.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XIII. The Use of a Concentrated Extract in the Treatment of Mold-Sensitive Patients

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SINCE October, 1947, we have treated approximately 200 patients sensitive to mold with concentrated Alternaria extract (Series 33) supplied by Dr. Prince. Prior to this extracts obtained from commercial sources were used for diagnosis and treatment.

Comparative scratch tests were used to assay the potency of the two brands. It was found that Alternaria 33 in a dilution of 1:200 (concentrated, labeled 1:50) gave comparable skin reactions to concentrated commercial extract (labeled 1:10). Hence we have continued to used the 1:200 dilution as the maximum concentration and have made dilutions in multiples of 10 (1:2000, et cetera). In the average case we begin treatment with a 1:200,000 dilution and rarely exceed a 1:2000 dilution in any case. That the extract is very potent is evidenced by constitutional reactions occurring when the patient's tolerance is exceeded by increase in dosage.

From our observations, we are certain this extract is diagnostically specific for Alternaria. It gives clear-cut positive reactions by scratch technique quite comparable to those given by strong pollen extracts. A large series of controls confirmed its specificity. Furthermore, the potency of different lots of extract remained quite constant, so that no difficulties were encountered in changing to a new batch of extract. This was in distinct contrast to our experience with commercial extracts, where a great variance in potency was observed. Indeed, an occasional lot would fail to exhibit any antigenicity as judged by skin test response. The uniformity of Alternaria 33 thus eliminates the difficulties usually experienced when a new batch of extract is received.

Statistical evaluation of our results is impossible at this time because of several factors. Of the 200 cases, only fifteen reacted to Alternaria alone. Criterion for diagnosis was a good clinical history correlating with positive skin tests. More than half of the group also reacted by skin test to Hormodendrum and Helminthosporium. Only recently have concentrated extracts of these been available, and we had to depend on unreliable commercial extracts. The majority of patients were mold and pollen sensitive, and it is difficult to assess the therapeutic value of the mold extracts in these combined cases. Furthermore, it has always been our practice to use no extract for diagnosis or treatment until it is evaluated on known sensitive patients as well as a control negative

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group. Hence, the advantages of the uniformity of the concentrate No. 33 were not apparent in our results from treatment.

On the basis of clinical experience and judgment, we believe the results from treatment with concentrate No. 33 were distinctly better than when commercial extract was used. This was more apparent in the fifteen cases of pure Alternaria sensitivity. We now have as much confidence in the therapeutic value of these concentrated extracts as in our own pollen extracts, where previously we were most uncertain about the therapeutic worth of commercial extracts.

Hence, we feel that we have been supplied with a uniformly potent Alternaria extract, free of irritative materials, that gives excellent results in the treatment of Alternaria-sensitive patients. It is so concentrated that we now require only one-fourth the amount of undiluted extract as when we relied on commercial sources. These factors, in addition to its specificity, have greatly simplified diagnosis and clinical management of the Alternaria-sensitive patient.

FIRST INTERNATIONAL CONGRESS ON ALLERGY

All those from North America and South America who plan to attend the First International Congress on Allergy at Zurich, Switzerland, September 23 through 29, 1951, should write to the Chairman of the Executive Committee of the International Association of Allergists, 424 La Salle Medical Building, Minneapolis 2, Minnesota, stating their preference for travel, whether by boat or plane, and how long they plan on being in Europe. The American Express Company has been appointed as the official travel agency for the Congress. The average time for the trip has been planned for two months, although shorter itineraries can be arranged to suit the individual. It is obvious that all arrangements made by an internationally known travel agency, the American Express Company with offices in all countries, will result in the highest type of service. If you prefer to make arrangements through your local travel agency, it will be satisfactory; the local agency will handle your trip through the American Express Company without additional cost to you. It is important that we get an approximate number of those who will attend from America and countries outside Europe. When planning your itinerary, it is important to know that it is almost impossible to go by boat and return by plane, or vice versa, because competition is so great that transportation lines refuse to issue a one-way ticket. You will soon be receiving a prospectus containing detailed information about the Congress. A representative of the American Express Company will be at a booth in the New Hotel Jefferson, St. Louis, during the annual meeting of the College.

PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY AND STABILITY DURING NEBULIZATION

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THE collection of aerosols of heterogeneous particle size of about 3 micra and below is complicated by the fact that these particles are too small to be trapped by liquids at room temperature. It became necessary during a recent study of the inhalation of aerosols of vitamin C to ascertain if the sodium ascorbate in the nebulizer was rapidly destroyed by the atomizing stream of oxygen which was used to generate the aerosol.[2] The residue of the sodium ascorbate in the nebulizer was readily obtained and titrated. There remained, however, the more difficult problem of collecting and titrating an aerosol of a substance presumably rapidly decomposed during nebulization by oxygen. Collection of the main fraction of the nebulized material by the technique herein described makes possible the establishment of a balance sheet of sodium ascorbate which was broken down incidental to the production and collection of the aerosol. In general, the dosage of labile aerosols may thus readily be ascertained.

Although there are estimates of the quantity of therapeutically active substances which actually are deposited in the lung during nebulization therapy, most of these disregard deposits in the upper respiratory tract. Studies attempting to establish minimum values for lung deposition of aerosols of various types are now in progress. Without the determination of aerosol stability in questionable cases, the procedure is made difficult.

METHODS

The centrifugal coil of Abramson and Demerec[3] was adapted by inverting the coil and changing the dimensions as follows: the length of the coil (Fig. 1) was 40 cm.; the radius of each coil was 1.25 cm.; the internal diameter of the tubing was 4 mm. The total length of the glass comprising the coil should be at least 3 meters. The actual size can readily be visualized from Figure 1 where a coil is connected with a DeVilbiss No. 40 nebulizer. It is most important that the coil be connected with a glass connection of the same diameter as the nebulizer itself. If this is not done, the large majority of particles are baffled out by the connection and the output of the nebulizer is diminished considerably by the intervening baffle.

With the present design, nebulization must be accomplished with a rubber stopper in the air vent in the side of the nebulizer. A leak of

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The phenolsulfonphthalein was especially prepared by Hynson, Westcott and Dunning.

The sodium ascorbate was kindly supplied by the Van Patten Pharmaceutical Co.

aerosol otherwise occurs because of the back pressure of the liquid in the coil as well as the resistance to airflow occasioned by the small diameter of the coil tubing. The collecting vessel illustrated in the figure was especially constructed to just fit the coil. The volume of liquid placed

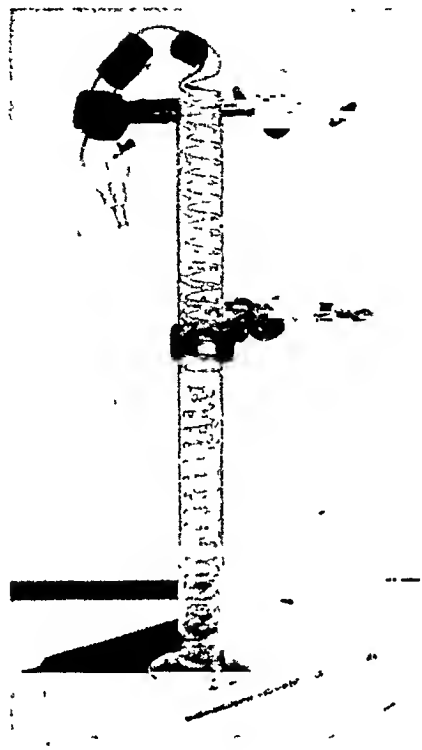

Fig. 1. Centrifugal coil for aerosol collection.

in the collecting vessel was 50 c.c. Even with this volume of liquid and numerous coils of small radii, not all of the aerosol was ever collected. A very faint mist was always seen emerging out of the liquid in the collecting vessel. This light mist which arises from the surface of the liquid is, however, quite negligible as far as our experimental results obtain. This is obvious not only from our experimental data, but is also evident from the geometry of the particle size distribution. The mass of any particle is proportional to the cube of the radius of the particle. The dose in a particle 0.1μ in radius is one thousandth the dose in a particle 1.0μ in radius. It is evident, then, that with the very small particles which escape the action of the coils, the weight loss is small.

The principle of the centrifugal coil is readily explained. The force F, acting on a particle moving in a circular path in a current of air is given by the equation:

$$F=M\ (V^2/r)$$

where M is the mass of the particle, V is the particle velocity, and r is the radius of curvature of the path. If the particle takes a circular path,

TABLE I. EFFECT OF INCREASING VOLUME VELOCITY OF AIR ON NEBULIZER DELIVERY

Initial Volume of Liquid: 2 c.c.

Time: 10 minutes

Corrected Airflow (Liters/min.) A	Initial PSP in Nebulizer (mg.) 1	PSP Condensed by Coil (mg.) 2	Residual PSP in Nebulizer (mg.) 3	PSP Delivered by Nebulizer (mg.) 4	Per Cent Delivery 5	Per Cent Loss of Delivered PSP 6	Mg. PSP Delivered Per Liter Airflow Per Min. 7
4.5	41.8	1.6	40.0	1.8	4.3	+9.5	0.040
5.2	41.8	2.4	39.5	2.3	5.5	—0.0	0.044
6.2	41.8	8.2	33.3	8.5	20.3	+4.1	0.138
6.9	41.8	11.7	30.5	11.3	27.0	—3.5	0.164
8.0	41.8	13.1	28.1	13.7	32.8	+4.4	0.172
9.4	41.8	16.3	26.0	15.8	37.8	—3.2	0.168
11.5	41.8	18.7	23.7	18.1	43.3	—3.3	0.157

TABLE II. EFFECT OF INCREASING CONCENTRATION OF SOLUTE ON NEBULIZER DELIVERY AT LOW VOLUME VELOCITIES OF AIR

Corrected Airflow (liters/min.) A	Initial PSP in Nebulizer (mg.) 1	PSP Condensed by Coil (mg.) 2	Residual PSP in Nebulizer (mg.) 3	PSP Delivered by Nebulizer (1-3) 4	Per Cent Delivery (4/1) 5	Mg PSP Delivered per Liter Airflow Per Minute (4/A) 6
4.0	4.2	0.6	3.6	0.6	14.3	0.016
4.0	19.0	2.6	16.0	3.0	15.8	0.072
4.0	22.0	2.6	18.7	3.3	15.0	0.080
4.0	36.6	4.9	31.4	5.2	14.2	0.124

TABLE III. EFFECT OF INCREASING GLYCEROL CONCENTRATION OF DELIVERY BY NEBULIZER

2 c.c. P. S. P. (11.2 mg.) at 5.7 L/min. for Ten Minutes

Per Cent Glycerol	PSP Condensed by Coil (mg.)	Residual PSP in Nebulizer (mg.)	PSP Delivered by Nebulizer (mg.)	Per Cent Delivery
0	2.9	8.1	3.1	26.9
10	2.9	8.2	3.0	26.9
15	2.8	8.2	3.0	25.0
20	2.6	8.5	2.7	24.1
25	2.3	8.2	3.0	23.2

therefore, with the velocity being held constant, the force acting on the particle is the greater, the smaller the radius of curvature of the path. This notion is not at all intuitive, as is clarified by the following examples: If two men stand at different points on the radius of a merry-go-round, it is evident that the one standing further from the axis of rotation will tend to be thrown off more than the one nearest the axis. Thus, the greater the linear velocity the greater the centrifugal force. This case is not analogous to the centrifugal fractionator since the linear velocity is kept constant. If, however, another example is used, the way in which the coil operates on aerosols is clarified. A train going around a track at a given velocity, say of 60 miles an hour, will not tend to be thrown off the track as much

if the track has a great radius of curvature as it would if the track has a small radius of curvature. In other words, the particles in the centrifugal fractionator act in much the same way as a train going around tracks of different radii of curvature with constant linear velocity. Other factors, such as the distances separating the coils of the fractionator, also play a role, but the treatment of these are beyond the scope of this paper.

The operation of the centrifugal coil, as adapted to the study of nebulizer delivery and aerosol stability, throws light on the behavior of the nebulizer under varied conditions. Although the construction of and the nature of the air jet, liquid feed and housing of the nebulizer lead to a certain degree of variation between nebulizers of the same construction, the data is of great interest in that the generalities derived from the data are qualitatively correct for all nebulizers of the type utilized.

Stock phenolsulfonphthalein in sterile ampules and vaccine bottles containing respectively 18 and 500 milligrams per c.c. of the dyestuff was diluted as indicated. Concentrations were checked against standards colorimetrically by the method described below. Solutions for volumetric determinations of sodium ascorbate were prepared according to directions in the United States Pharmacopeia No. XII.

Phenolsulfonphthalein determinations were made with the Klett-Summerson photoelectric colorimeter (Filter: 54 K-S), using standards prepared from the 6 mg. commercial ampules. The dye solutions were alkalinized with 5 c.c. per liter of 5 per cent potassium hydroxide. The limit of error was approximately 5 per cent.

The same DeVilbiss No. 40 nebulizer was used in any single series of experiments given in the tables. Different nebulizers were used for different series of experiments. The data from table to table are therefore qualitatively, but not quantitatively, interchangeable.

The airflow was corrected by determining the rate of airflow from the mouth of the nebulizer using a Precision Wet Gas Test Meter manufactured by the Precision Scientific Company. Correction was thereby automatically made for the increased resistance to flow velocity incurred by the decreased tube diameter of the centrifugal coil.

Sufficient solution was used so that the jets produced the same quantity of aerosol per unit time at the beginning and at the end of the experiment. The quantity of phenolsulfonphthalein given in Column 1 of Tables I, II and III was dissolved in 2 c.c. of normal saline.

Experiments lasted for ten minutes with the gas air pump or an oxygen cylinder. The stability experiment with sodium ascorbate in Table IV lasted fourteen minutes with an oxygen flow of 5 liters per minute.

The centrifugal apparatus is depicted in Figure 1. The test solution was added to the nebulizer, the gas turned on and permitted to run for the prescribed time with the vent closed. The equipment train was then broken at the rubber-glass connection closest to the nebulizer. This point

separates the nebulizer residue from the coil condensate. The coil was then washed three times with distilled water and the washings diluted to one liter after the addition of 5 c.c. of 5 per cent potassium hydroxide. This is the coil condensate of Column 2, Tables I and II. Care must be

TABLE IV. FRACTIONAL CONDENSATION OF APPROXIMATELY 20 PER CENT SODIUM ASCORBATE

(1 c.c.=18.9 c.c. N/10 Iodine)

Time Nebulized	N/10 Iodine
2 min.	0.56
4 min.	0.56
6 min.	0.62
8 min.	0.59
10 min.	0.62
12 min.	0.48
14 min.	0.61

Nebulized	4.04 c.c.	of Sodium Ascorbate recovered from coil.
Nebulizer residue	13.94 c.c.	
TOTAL	17.98 c.c.	or a loss equivalent to about 1 c.c. of N/10 Iodine.

taken to collect all of the dyestuff at the various rubber-glass connections, since a small loss may produce a larger error in this part of the procedure. The nebulizer was then washed so that no color resulted upon the addition of alkaline wash water. These washings were diluted to 1 liter after the addition of 5 c.c. of 5 per cent potassium hydroxide. This represents the nebulizer residue of Column 3, Tables I and II. Determinations on the liter washings are run with aliquots, so diluted as to bring the concentrations within the range of the standards employed.

The experiments with sodium ascorbate, Table IV, were performed similarly except that the coil condensate was determined separately at various time intervals noted. The nebulizer residue was estimated at the conclusion of the experiment.

RESULTS

Column 6 of Tables I and II show a spread of the per cent loss of Initial PSP from — 1.0 per cent to + 3.4 per cent. This is well within the limits of experimental error. The effect of volume velocity on collection efficiency is likewise negligible since the per cent loss goes from + 0.4 per cent at 4.5 liters per minutes to — 1.4 per cent at 11.5 liters per minute. This negligible loss results despite the fact that a faint mist of aerosol is always seen leaving the coil.

Effect of Increasing Volume Velocity on Nebulizer Delivery.—Table I indicates that the per cent delivery rises from 4.3 per cent at 4.5 liters per minute to 43.3 per cent delivery at 11.5 liters per minute, with condi-

tions otherwise being constant. The efficiency of nebulization does not follow the same quantitative trend, since the output expressed in milligrams of PSP delivered per liter airflow per minute (Column 7) approaches a maximum at about 7 liters per minute. In this experiment it decreased slightly with the highest air velocity. However, this decrease is not marked. With this nebulizer the efficiency increases between 5.2 and 6.2 liters per minute. Very effective use of the nebulizer is at about 10 liters per minute. (Nasal tips are needed.) Various nebulizers differ in their points of maximum efficiency.

Effect of Increasing Solute Concentration on Nebulizer Delivery.—With constant velocity of airflow, increasing the PSP concentration from 4.2 mg. to 35.6 mg. showed no influence on the per cent delivered. (Table II.) However, the total PSP delivered by the nebulizer (Column 4) increased from 0.6 mg. with 4.2 mg. per c.c. initially to 5.2 mg. delivery with 36.6 mg. per c.c. initially. The milligrams of PSP delivered per liter per minute likewise rose from 0.016 to 0.124 mg. per liter per minute.

Effect of Increasing Glycerol Concentration on Nebulizer Delivery.—It is common clinical practice to use glycerol as a vehicle in nebulization therapy. The effect of glycerol is illustrated in Table III. With increasing concentrations of glycerol, the per cent delivery hardly changes, whereas the coefficient of viscosity approximately doubles at a concentration of 25 per cent glycerol.

Sodium Ascorbate Stability during Nebulization with Oxygen.—At the beginning of the experiments with vitamin C the authors employed ascorbic acid. The solutions were found to be irritating to patients. This was due to the low pH. Sodium ascorbate was substituted and found not to be irritating even in concentrations up to 20 per cent. The coil experiments were subsequently carried out with sodium ascorbate. The data appears in Table IV. It is noted that after fourteen minutes, 21.3 per cent of the original sodium ascorbate has been collected by the centrifugal coil with a loss of approximately 5 per cent, or about 0.05 c.c., of the original 1 c.c. solution of sodium ascorbate placed in the nebulizer.

The results dealing with delivery of the dye are directly applicable to clinical usage. In order to increase dosage of nebulized medication and hence increase the therapeutic efficiency and shorten the time of therapy the following points are of importance:

1. Increase velocity airflow. A practical level is 10 liters per minute, with nasal tips similar to the DeVilbiss No. 640.

2. Increase concentration of medication.

In increasing the velocity of airflow to 10 liters per minute the oral method of administration may be irritating. It was found that the De-

Vilbiss nasal tips which permit administration of aerosols, resulted in lessened or no irritation at the higher velocities of airflow and concentration. A shortened time for therapeutic aerosol delivery is, of course, obtained. This procedure makes certain that the aerosol is delivered exactly at inspiration because the mouth is closed and air reaches the patient only through the nebulizer. In this way we have been administering solutions containing approximately 1,000,000 units of crystalline penicillin G per c.c. The patient is much more comfortable and co-operative with this shortened procedure. It has not been decided whether open or closed vents are desirable in therapy.

A series of subjects have received 10 and 5 per cent PSP for fifteen minutes at 10 liters per minute, with nasal tips. Utilizing the principles put forth in this paper, PSP is being tested, at present, as a chemical indicator in experiments in man. It may be stated that this method shows promise as a means of studying the behavior of antibiotic aerosols in the lungs, bronchi, and systemically, and also as a possible lung function test. A full report of these experiments will appear in a subsequent paper now in preparation.

The data of Table IV shows rather surprisingly that during the nebulization of this high concentration of sodium ascorbate, a comparatively small amount of decomposition of the sodium ascorbate occurred in the presence of oxygen. Dilute solutions of sodium ascorbate showed the expected rapid decomposition of vitamin C which can be readily followed by the same procedure. Diverse properties of medical significance have been ascribed to vitamin C. Among these are anti-viral activities, enzyme inactivation, formation of collagen in connective tissue, and acceleration of fibrosis in the therapy of tuberculosis. Our procedure shows that it is feasible to employ vitamin C as an aerosol for topical therapy in suppurative and other infectious pulmonary diseases, provided that sufficiently high concentrations are used.

Preliminary experiments indicate the 15 per cent sodium ascorbate may be inhaled for fifteen minutes as an aerosol without irritation by patients with severe asthma. A 10 per cent solution can be given six times daily without irritation. In all likelihood, higher concentrations could probably be used.

SUMMARY

1. A centrifugal coil which efficiently condenses aerosols produced by commonly used nebulizers is described.

2. The effects of volume velocity, initial concentration, and viscosity of the liquid in the nebulizer, on delivery by the nebulizer, are discussed on the basis of quantitative data.

3. It is shown by this procedure that sodium ascorbate aerosol, nebulized

(Continued on Page 638)

PENICILLIN SENSITIVITY

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WITH the widespread use of penicillin in otolaryngology, a significant number of patients will manifest allergic reactions to this drug, and the problem of management of such reactions is of practical importance. Just as in the case of the sulfonamides, there is ample evidence that penicillin is being used indiscriminately. We have encountered a number of instances in which it was used unnecessarily in the treatment of the common cold and was followed by the typical serum-disease-like reaction, with generalized urticaria and angioneurotic edema. In many cases of infection encountered in otolaryngology, the severity is not sufficiently marked to indicate the use of penicillin.

The most common type of reaction manifested to penicillin simulates serum disease. It is characterized by the same incubation period of seven to ten days, followed by urticaria, angioneurotic edema, itching, fever, and joint pains. In some instances, the symptoms may be mild and transitory, and they may be readily controlled by the administration of the antihistaminic drugs. On the other hand, very severe reactions may occur which are not controlled by the ordinary methods of treatment.

Since the advent of the therapeutic use of penicillin, the literature has become replete with articles dealing with the occurrence of untoward reactions. Most of the pertinent information has been recently reviewed and summarized in a few important presentations which will be outlined below. For further details, one may consult the papers of Peck and his associates,[2] Prince and Etter,[3] and the review of the literature by Epstein and Macaulay.[1]

According to Peck, there are two distinct types of reaction to penicillin: (1) the serum-sickness-like urticarial type which is an induced sensitivity, and (2) the eczematoid-trichophytid-like type which may be based upon a previous sensitivity produced by a fungous infection. The so-called "spontaneous" penicillin-sensitive cases belong to this latter group. Exfoliative dermatitis following penicillin administration appears to be of rare occurrence and of the mild type.

Although reactions may occur to either the commercial preparations or the pure crystalline types, they appear to be more common to the former. On the other hand, it has been shown that reactions may occur from the impurities in commercial preparations and not the penicillin itself.

Besides the parenteral route, other routes of administration must be considered. There is considerable difference in the sensitizing potential where penicillin is applied to different areas of the skin and mucous membranes. The face and mouth particularly appear to be more sus-

ceptible. Penicillin aerosol, used for respiratory infections, has resulted in stomatitis, nasal irritation, and dermatitis around the nose and mouth in about 5 per cent of the cases. Stomatitis from oral administration occurs in about 14 per cent. On the other hand, the incidence of penicillin reactions in the vaginal and rectal mucosa have been almost nil.

Epstein and Macaulay point out that if a reaction occurs during parenteral penicillin therapy, it does not necessarily indicate that penicillin may not be tolerated at a later date. Sensitivity may be of relatively short duration and may decline rapidly. It may decrease over a period of six to twelve months so that a second course may be taken without reaction. The interval may be shorter, but it is rarely less than six weeks. On the other hand, each subsequent attack may tend to increase the degree of sensitivity, with an increase also of the severity of the reaction. In these cases, the patient should be given small trial doses. The intradermal test may be positive and yet the patient may tolerate intramuscular injections.

THE CLINICAL PROBLEM IN PENICILLIN SENSITIVITY

Peck and his associates report their observations on tests for penicillin and trichophytin sensitivity in a group of 406 adults and ninety-one children.

Material Methods.—Intradermal tests:

(a) 0.01 to 0.02 c.c. of 5,000 units per c.c. amorphous penicillin; read in fifteen to twenty minutes for immediate reaction.

(b) 0.10 c.c. intradermal, 2,000 units or 1.2 mg. in .10 c.c. isotonic sodium chloride; delayed type of reaction is read in forty-eight hours or later.

If commercial amorphous penicillin is used, re-check positive reaction to crystalline penicillin. Amorphous preparations may give nonspecific reactions.

(c) Trichophytid test: 1-30 dilution in 0.10 c.c. isotonic sodium chloride.

The Delayed (forty-eight hour) Cutaneous Test.—This is a reliable index of penicillin sensitivity. The reaction is similar to the trichophytin test. A positive reaction is characterized by an area of erythema with edema and infiltration, usually about 1 cm. in diameter. It may be larger and studded with small papules or even vesicles. Local pruritus is common with the reaction. In some instances of high degree of sensitivity, positive reactions may be noted with 2 to 5 units.

The Patch Test.—This is not of much value.

Immediate Intradermal Test.—All reactions were negative on ninety-two subjects (Peck).

CLINICAL REACTIONS

According to Peck, two major types of penicillin reactions are most commonly encountered: (1) reactions of the urticarial serum-sickness-like type, in which sensitization is induced by treatment; (2) reactions with an erythematovesicular eruption, resembling the trichophytids.

Type 1. Reactions of the Urticarial Serum-sickness-like Type.—Urticaria and erythema with joint pains and sometimes fever, occurring after a definite incubation period (seven to twelve days), characterize the most common type of allergic reaction to penicillin. In some instances, reactions may occur within several days; in others, they may be delayed as long as three weeks. In severe cases, there may be angioneurotic edema, asthma, pulmonary infiltration and hyperpyrexia. Reactions occurring after the second or subsequent administration may be of the accelerated type, occurring with a short or no incubation period. Most reactions follow intramuscular injection, but may also follow oral administration.

Although a positive penicillin reaction is helpful in confirming sensitivity, a negative reaction does not exclude sensitivity. When several medications are administered, the test is useful in determining which drug is responsible for the eruption. The incidence of test skin reactions is greater in those patients who have had penicillin previously. In a group of ninety-eight patients, observed by Peck, who had received penicillin without reactions, not one reacted positively to the cutaneous test. Among 130 patients who received penicillin, seventeen (13.4 per cent) showed positive cutaneous reactions. Among those who had not had penicillin, the incidence of reactions was 5 per cent. All of the above seventeen patients who reacted were men (general ratio: 3 to 1). Positive reactions may become negative later. The majority of patients gave no history of allergy. The incidence of penicillin reaction is very low in children.

If the penicillin reaction has been mild, the readministration may be accompanied by epinephrine or antihistamine drugs. Substitute medication with sulfonamide drugs might be preferable. In sensitive patients, small doses of 2,000 to 3,000 units at six-hour intervals may be tried first, then gradually increased. It is unwise to give large doses in cases where previous reactions occurred or where positive cutaneous tests were present. On the other hand, induced sensitivity is only temporary, and a later administration may be well tolerated without reactions.

Type 2. Reactions with Erythematovesicular Eruptions, Trichophytid Type.—The latent stages characterized by a positive reaction in the absence of previous administration of penicillin.

The active stage is based on a pre-existing latent sensitivity. There is an erythematovesicular reaction which tends to localize on the hands, feet and groins. It may become a generalized exfoliative dermatitis.

MECHANISM OF SPONTANEOUS SENSITIVITY

Latent penicillin sensitivity is apparently associated with previous fungus infection. Skin sensitization to penicillin takes place in much the same way as sensitization to trichophytin.

DESENSITIZATION TO PENICILLIN

Desensitization before readministration of penicillin is more frequently necessary with Type 2 than with Type 1 sensitivity.

DESENSITIZATION SCHEDULE FOR SUBCUTANEOUS ADMINISTRATION (PECK ET AL)

Injection	*Number of Units*	*Intervals*
1	200	
2	400	Injections every 2 to 3 days.
3	800	
4	1200	Injections daily.
5	1600	
6	2000	May be necessary to
7	2500	
8	3000	start with 50 units.
9	5000	
10	10,000	With local reaction or fever,
11	15,000	
12	20,000	reduce dose to nonreactive point.

Oral Desensitization—Start with 1,000 units per day and gradually increase following precautions as recommended above.

ROUTINE TESTING OF OFFICE PATIENTS

As a matter of record, it is suggested that all new patients and all previous ones who return for observation should have the cutaneous test to penicillin. In the event that the administration of penicillin is necessary at a later date, one knows how to proceed with treatment and possibly avoid many severe reactions.

MANAGEMENT OF URTICARIA AND ANGIONEUROTIC EDEMA RESULTING FROM REACTIONS TO PENICILLIN SERUM AND OTHER AGENTS

While we are concerned for the moment with urticarial or serum-disease-like reactions to penicillin, the principles of treatment outlined below apply also to reactions from serums and other allergenic substances. These methods of therapy are also applicable to cases of unknown etiology.

The milder types of reaction may disappear very promptly without any treatment whatsoever. The more marked reactions usually respond to the administration of an antihistaminic drug or epinephrine.

The severe types, with generalized urticaria and angioneurotic edema as well as other complications, do not respond to the ordinary types of therapy; thus, more heroic and intensive types of therapy must be employed.

SPECIFIC IMMUNIZATION

For the treatment of acute urticarial reactions, Rinkel found that satisfactory relief could be obtained by the administration of 1 to 2 units of penicillin intradermally every one or two days.

HISTAMINE THERAPY

Based on a group of nine patients with severe foreign protein type of reactions (eight to penicillin and one to horse serum), most of whom failed to respond to other forms of therapy, Prince and Etter have reported their observations on the use of intravenous and intradermal histamine. All patients showed clinical improvement. It was pointed out that no definite dose or rate of medication can be established; each patient presents an individual problem.

Prince and Etter recommended the intravenous administration of histamine as the method of choice, as the dose and side effects can be readily controlled by the rate and amount of the infusion. All or part of a solution of 250 c.c. of saline or 5 per cent glucose, containing 2.75 mg. of histamine acid phosphate (1 mg. histamine base), is given at first to determine the patient's degree of tolerance. The rate of injection is regulated so as to produce a generalized flush. If given too rapidly, headache and substernal pain may be induced. The average interval between injections was found to be about six to eight hours. In some cases, continuous infusion or a stronger solution, such as 5.5 mg. per 250 c.c. of vehicle, may be necessary.

Intradermal administration was found to be very useful by Prince and Etter, especially in those instances in which intravenous therapy was not satisfactory, and also in patients in whom it was difficult to locate the veins and in the treatment of children. This method must be used with caution, as treatment cannot be discontinued at will as in the case of the intravenous. Small intradermal injections should begin with 0.10 c.c. of a solution containing 2.75 mg. per 5 c.c. (or 1-5,000) and increased as indicated. When larger doses are required, histamine dihydrochloride, 1-100, may be given in doses of 0.05 to 0.10 c.c. The idea is to determine the dose which will produce a flush for a period of one-half to two hours. When properly regulated, there appears to be no danger from the use of histamine therapy of this type.

This method of treatment requires hospitalization, and the therapy must be instituted by responsible personnel.

NONSPECIFIC TREATMENT WITH STAPHYLOCOCCUS TOXOID

Nonspecific therapy has always had a place in allergy, especially in those cases in which everything has been tried without results. It is a well-known fact that allergic reactions are counteracted by tissue injury or shock. A fracture, a burn, fever, a surgical procedure, a local or general reaction from a vaccine will produce this effect, as manifested, for

example, by the disappearance of urticaria, nasal allergy or bronchial asthma at least for an indefinite temporary period of time.

From time to time we have encountered many cases of severe acute and chronic urticaria and angioneurotic edema in which every therapeutic means of management was tried without satisfactory results.

After groping around among various possible nonspecific agents, it was decided to try small doses of staphylococcus toxoid.

Preparation Used.—

Staphylococcus Toxoid 100 units per c.c.

Dilute 1-10 as follows:

1 c.c. (100 unit stock) plus 9 c.c. saline = 10 c.c. — 10 units per c.c.

With 10 units per c.c. solution, 1 unit = 10 c.c.

Range of dosage: 1 unit to 20 units

Intervals: 3 to 4 days, later 7 to 10 days.

Treatment may be started with a dose of 1 to 2 units. If only slight or no effect is noted, this can be increased to 2, 3 or even 5 units. When the effective dose is determined, it is not changed, but the intervals are increased. If seven- to ten-day intervals are obtained with no symptoms, treatment should be discontinued.

In several instances of severe acute penicillin urticaria, 1 to 2 units were effective in giving relief within twelve hours. Sometimes only a few treatments are necessary.

In a patient with continuous urticaria of twelve years' duration, response was immediate to 20 units. The dose was immediately reduced to 1 or 2 units at five- to seven-day intervals. The patient is now free of symptoms after one month of treatment.

In another patient, a chronic urticaria of two years' duration cleared within one week. In several other cases of the chronic type, with no known etiology, response to treatment was satisfactory.

This method has been consistently effective in the relief of severe penicillin reactions, often requiring only a few injections at three- to four-day intervals.

REFERENCES

1. Epstein, S., and Macaulay, W. L.: Progress in allergy: allergic skin diseases. Ann. Allergy, 6:442-480, 1948.
2. Peck, S. M.; Siegal, S.; Glick, A. W.; Kurtin, A., and Bergamini, R.: Clinical problems in penicillin sensitivity. J.A.M.A., 130:631-640, 1948.
3. Prince, H. E.: Histamine treatment of foreign protein type reactions. Ann. Allergy, 6:386-392, 1948.
4. Rinkel, H. J.: Personal Communication.

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INHALANT ALLERGY

I. The Whealing Response of the Skin to Serial Dilution Testing

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IN 1941 Hansel[1] published an article on small pollen dosage which recreated interest in two phases of inhalant allergy.

First was the fact that certain patients could obtain relief with small doses. This was in contrast with the fact that many patients had received good results with the larger doses which had always been used. His findings not only indicated that inhalant allergies varied in degree in successive patients but implied that in the same individual sensitizations to the different antigens could be expected to differ. This clinical observation emphasized the need for not only determining to which inhalant the patient was sensitive, but to also ascertain the degree of each of these sensitivities. This can be done by some form of serial dilution testing.

Second, his paper stimulated further interest in coseasonal treatment.

In the course of a clinical appraisal of Hansel's method of titration and treatment with individualized dosage, I have employed serial dilution testing (titration) on every patient seen during the past eight years. In the course of this study certain features of the whealing response of the skin to such tests were revealed. I believe these are of sufficient importance to justify this communication.

TECHNICAL DATA

All our extracts are made in 50 per cent glycerine and Coca's solution.

Pollens are prepared for testing in genetic groups; all other inhalants are made up individually. No foods have been used.

The diluting fluid is normal saline with 0.4 per cent phenol added.

Dilutions are made in the ratio of 1:5 since these are more nearly approximate to the sensitivity of the skin than are the 1:10 dilutions. These solutions are made new every two weeks. It has been found by testing that there is a measurable deterioration by the fourth week and a possible loss of potency by the third week.

These dilutions are numbered from No. 1, the weakest, to No. 9, the strongest. The No. 1 is approximately a 1:40,000,000, and the No. 9 is a 1:100 dilution. The No. 10, or Concentrate solution, is a 5 per cent solution by weight volume. It has been shown by these tests that there is no essential difference between a 3 and a 5 per cent solution. In Table I, I have indicated the various dilutions, the number used to designate each dilution and the approximate dilution of the antigen in these different solutions.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

Name JONES Date 2-11-46 Tester R Dgs PNA + S.H.F.

ANTIGEN	000	00	0	1	2	3	4	5	6	7	8	9	A'mt	No.	Set
Ragweed Mix.				5	5	5	5	5	7-25	9-30					
Rag. Repeated								5	7-25	9-30					
Sagee															
Ive Cilieta							5	5E	7-25						
Pigweede										7-25	9—				
Pig. Repeated															
Kochie															
Chenepode															
Thistle															

Fig. 1. A special chart used to post results of testing. Wheals without erythema are posted with numerals indicating their size in millimeters. Wheals with erythema are posted with two numerals, the first indicating the size of the wheal, the second the amount of erythema.

TABLE I

Dilution	Number used to Designate This Dilution	Approximate Dilution of Antigen
Concentrate	10	1:20
1:5	9	1:100
1:25	8	1:500
1:125	7	1:2,500
1:625	6	1:12,500
1:3,125	5	1:62,500
1:15,625	4	1:312,500
1:78,125	3	1:1,562,500
1:390,625	2	1:7,812,500
1:1,953,125	1	1:39,062,500
1:9,765,625	0	1:200,000,000
1:48,828,125	00	1,1,000,000,000
1:244,140,625	000	1:5,000,000,000

In some instances it is necessary to use the 0, 00 and 000 solutions, but these are not ordinarily kept made up. They are not needed more than once or twice yearly, hence it would not be practical to either prepare them or to use them routinely. On one occasion I have had a patient respond with a 15 mm. wheal to the triple-zero dilution of house dust and be nonreactive to the control. The end point of reaction to pollen and animal danders varied between Solutions 4 to 8.

It has been found of great practical value to use numbers in reference to solutions rather than their actual numerical dilutions. Furthermore, it is easier to discuss this type of testing and the results when these solutions are numbered in the order of their application, rather than the oft used method of designating the strongest solution as No. 1.

The amount injected is 0.01 c.c. This will produce a 4 mm. wheal when injected at the proper depth. This wheal should be pale and sharply demarcated. The results of the tests are more apt to be modified by the depth of the injection than by inability to measure exactly 0.01 c.c.

Readings are made at the end of ten minutes and are posted on special sheets as shown in Figure 1. The negative responses are given in numerals indicating the diameter of the wheal in millimeters. This is

usually 5, sometimes it is 6. When the wheal is erythematous, instead of pale, but without a zone of erythema about it, this is indicated by the designation of 6E or 7E as the case may be.

When the reaction is characterized by a zone of erythema about it, this is indicated by using two numerals, separated by a dash. The first number refers to the diameter of the wheal, the second to the diameter of the erythema. A posting of 7-25 would mean then, that the wheal was 7 millimeters and the erythema was 25 millimeters in diameter. If one does not wish to post erythema, its occurrence is indicated by using the numeral for the wheal, followed by a dash, as for instance, 9—.

Occasionally tests increase in size between ten and twenty minutes, and when so, these are posted with the letter "D" before the numerals, for instance, D11-30. These late and increased reactions are considered under certain conditions. Some patients will always show an increase after ten minutes; others never do, and still others will show this only with certain antigens. It has been found that when the end point moves from one dilution to another in delayed reactions they are of significance. If one is in doubt, err on the side of accepting the weaker reactor as being the end point. These delayed reactions are found mostly on original pretreatment testing.

Finally, and this is extremely important, the testing and the therapeutic solutions are to be made from the identical lots of the same material.

TYPES OF RESPONSE TO SERIAL DILUTION TESTING

All reactions may be classified under two distinctive forms. First are those having one or more absolutely negative tests, followed by a distinct reaction of whealing, erythema and then progressive whealing, usually through three dilutions. This is called the clear-cut end point type of reaction.

The second form of response has erythema with every test applied.

Tests with Clear-Cut End Point of Reaction.—In this type of reaction there will be one or more tests which have given a 5 mm. wheal without erythema, and then the next stronger dilution will produce a reaction characterized by two features: first, there is a zone of erythema about the wheal, and second, the wheal is 7 millimeters in diameter (or two millimeters larger than the non-reactor or the control). The next two tests will invariably show progressive whealing, usually being 9 and 11 millimeters in diameter, but the erythema remains about the same. This type of response is illustrated in Figure 2,A. This is the nature of the skin response in approximately 72 per cent of all tests applied in our patients.

There may be deviations from this "normal" response, either in the wheal size or in the occurrence of the erythema. For instance, one may obtain a response of several 5's, then get 6-20, 8-30 and 12-30. Again,

one may have a response of several 5's, then get 5-20, 7-25, 9-30 and 11-30 (Fig. 2,B).

Whealing is invariably progressive with the first three dilutions, including the one producing the end point of reaction, but in some cases there

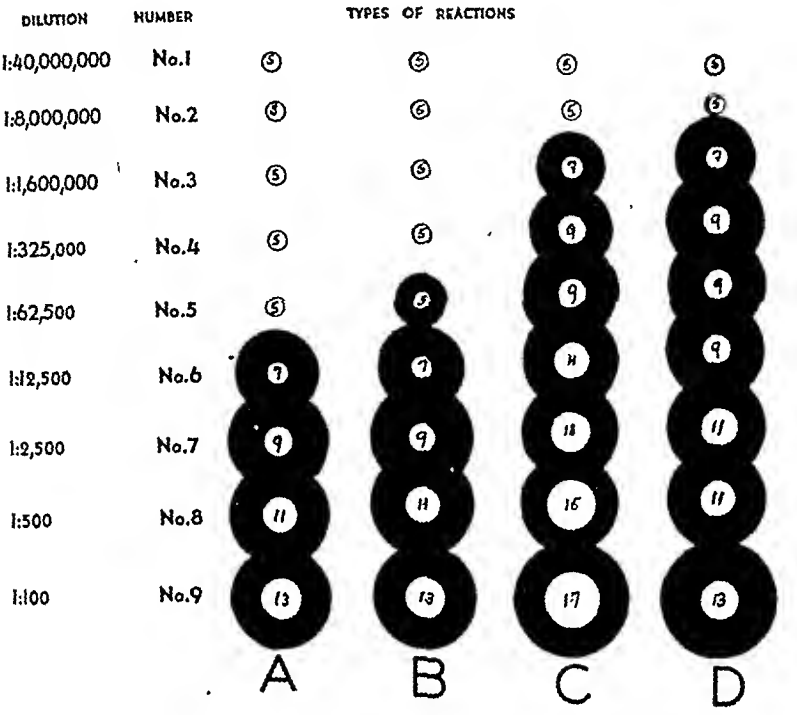

Fig. 2. A diagrammatic representation of reactions with clear-cut end points. (A) End point with both erythema and 7 mm. wheal occurring on same dilution. (B) End point with erythema occurring with 5 mm. wheal, followed by 7-25 reaction and progressive whealing. (C) End point with both erythema and 7 mm. wheal occurring on same dilution, but whealing is identical on the second and third reacting dilutions. This is a short plateau. (D) End point with both erythema and 7 mm. wheal occurring on same dilution, with identical size wheals on the next three dilutions. This is a long plateau.

are one or more 5's, then 7-20, 9-30, 9-30 and then 11-30. This phenomena of different strength solutions causing identical sized wheals is called the plateau of the reaction, and it may be short (Fig. 2,C) when due to two dilutions, or it may be long when due to three dilutions or even more at times (Fig. 2,D). These two reactions suggest concomitant and complicated sensitizations. These are often, but not necessarily always, associated with food allergy.

Reactions with Erythema on All Dilutions or Linear Erythema Responses.—As the name suggests erythema is present on the first test applied, regardless of the wheal size. There are several modifications of this type of reaction.

1. Straight linear erythema response: In this reaction there are several tests all reading 6-25 or 7-25 and then there is an 8-30 or a 9-30 reaction followed by progressive whealing. The end point of reaction

in this test is the dilution which initiates progressive whealing (Fig. 3,A). This reaction is not due to dermographism since one can obtain both the clear-cut end point type of reaction and the linear erythema response side by side at the same time in a given patient. Actually, only 3 per

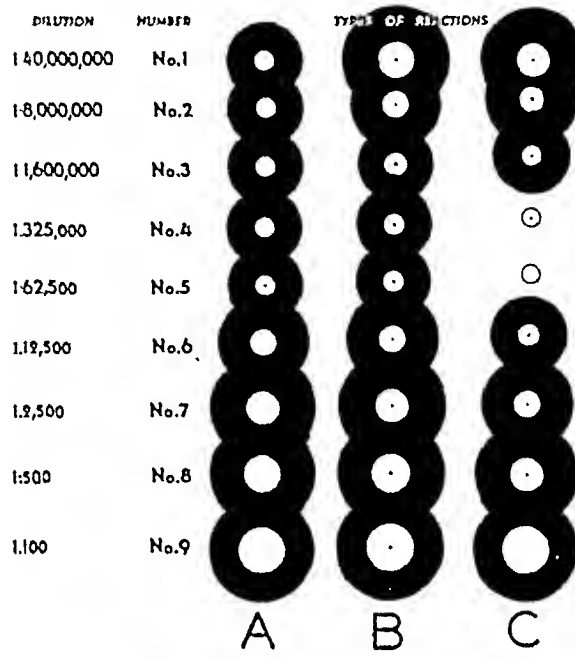

Fig. 3. A diagrammatic representation of responses with erythema on the first test applied. (A) Straight linear erythema response, having several identical size wheals and then develops progressive increase in size of wheals. (B) Hour-glass linear erythema reaction, whealing and erythema having the configuration of an hour glass. (C) Hour-glass linear erythema response with clear central zone.

cent of the patients have dermographic skins; that is, every test applied including the control has erythema about the wheal.

2. The hour-glass linear erythema response: In this test the configuration of the erythema and the wheals simulates an hour glass. The usual readings are, 12-35, 9-30, 8-25, 7-25, 7-25, 9-30, et cetera. The end point of reaction is the 9-30 reaction (Fig. 3,B).

3. Hour-glass reaction with clear central zone: This reaction is not due to technical error as I first thought (Fig. 3, C). There is decreasing whealing and erythema for several dilutions, then one or more tests with absolutely no reaction, then progressive whealing with erythema. The end point of reaction is the first solution producing whealing and erythema after the clear zone.

TERMINOLOGY

Two terms which have been used in this communication should be defined in more detail.

First is the "end point of reaction." This may be defined as being

the first dilution which initiates progressive whealing and *is also* 2 millimeters larger than the preceding or the non-reacting tests, one or the other, as the case may be. In the clear-cut end point reactions this test will usually be the first to show erythema, unless erythema is obtained with a 5-20 reaction, then it would be the first wheal to attain the 7-20 size. In the linear erythema reactions the end point is the first solution to initiate progressive whealing. In the hour-glass reactions with the clear central zone it would be the first solution below the clear zone *which is followed by* progressive whealing.

The second term is the "multiple" or as often stated, "the multiple of the end point." To obtain this, the treatment dose is computed in terms of the solution giving the end point and then is divided by the test dose. (This is always 1.) Example: If the end point was on the No. 6 dilution and the dose is 0.10 c.c. of the No. 7 dilution, this would be a multiple of 50. (0.10 c.c. of the No. 7 would equal 0.50 c.c. of the No. 6 solution.) The multiple of 50 when the end point is on the No. 6 solution could be any of these four doses: (1) 2.50 c.c. of the No. 5, (2) 0.50 c.c. of the No. 6, (3) 0.10 c.c. of the No. 7, or (4) 0.02 c.c. of the No. 8.

If the end point is on the No. 3 dilution and the patient is receiving 0.25 c.c. of the No. 5 dilution, this is equal to 6.25 c.c. of the No. 3 solution; hence the multiple is 625.

The statement of the treatment dose in terms of the "multiple" is a convenient means of giving the therapeutic dose in relation to the end point of reaction and is a comparative expression of the end point of reaction and the necessary dose.

SUMMARY

The clinical implications of the types of response to serial dilution testing should be so obvious as to require little explanation. However, certain points might be emphasized.

The clear-cut end point reactions present little error in interpretation. One should not mistake the occurrence of erythema without a concomitant increase of whealing as the end point of reaction.

The possibility of making an important clinical error in the interpretation by using only a single or two solutions in testing is more likely in the case of the linear erythema reactions.

In the case of the hour-glass reactions, with a 12-30 response on the No. 1 dilution and only a 7-25 on the No. 5, one could interpret this large initial whealing of the skin to indicate a very high degree of sensitization if the various types of skin response are not known. It can easily be seen that the results of therapy based upon such misinterpretation of skin testing would be ineffective.

It would seem that the minimal requirement in the use of intracutaneous

(Continued on Page 650)

INHALANT ALLERGY

II. Factors Modifying the Whealing Response of the Skin

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IN A PREVIOUS communication[2] the nature of the whealing response of the skin to serial dilution testing was described in detail. In this paper the factors which modify this response will be discussed in light of our present knowledge.

TERMINOLOGY

There are four terms used in this paper which should be delineated at this time.

First is that of "vertical testing." This refers to the application of tests of various antigens, all of the same numbered dilution. Normally, this is done in preseasonal testing, but may also be done in coseasonal application of serial dilution tests (titration). It refers to the fact that the same strength material is used of *several different* antigens.

Second is that of "linear testing." This refers to the application of various numbered dilutions of the same antigen. This is the usual procedure when one is attempting to determine the end point of an antigen.

Third is that of "shift to the left." This term is used when the end point moves towards the No. 1 dilution.

Fourth is that of "shift to the right." This term is used when the end point moves towards the No. 9 dilution.

TREATMENT

Treatment, or so-called hyposensitization, is the most definite single factor which affects the whealing response of the skin. The effect of therapy may be either very rapid, often with one or two doses, or it may be gradual, such as occurs with the generally accepted plan of dosage over a period of time.

The effect of specific treatment upon the whealing produced by an antigen will vary according to the time when an evaluation is made of such possible effects. In this discussion, the figures have reference to ragweed and pigweed sensitive patients in seasons, after treatment with their primary and secondary pollen allergies. It has been found that under these conditions approximately 43 per cent of the patients have a definite decrease in their whealing response. At times the end point will shift one or two dilutions to the right. Approximately 36 per cent have no particular change in their test reactions, while 21 per cent have a definite increase in their whealing, or a *shift to the left, sometimes as much as five dilutions.*

In the preceding paragraph the changes discussed were those which oc-

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curred after preseasonal treatment with continuation of coseasonal therapy until the tests were repeated. These are, therefore, the results of prolonged treatment. There is, however, a somewhat more dramatic and rapid effect, which when it occurs with one or two doses is termed "flash response."

The term "flash response" refers to reactions as illustrated in the following case reports: A patient was tested with the No. 8 dilution of pigweed out of the pollen season and without any previous therapy. The reaction was a 13-45 response in ten minutes. This would ordinarily be evidence of a high degree of sensitivity, but when the weaker dilutions were applied the following day, it was found that there was no reaction until the No. 7 dilution, and a repetition of the No. 8 dilution only produced a 9-30 reaction. This then is a "flash response."

A second patient gave a 35 mm. wheal to the No. 8 dilution of Alternaria. When linear testing was done, the end point was found on the No. 4 solution. There is a discrepancy of 20 mm. between the No. 8 test of the first day and the end point. This, too, is a "flash response."

"Flash responses" concern not only those who titrate but also those who use ordinary scratch tests. It is imperative to have all scratch tests repeated. The second day's tests are more likely to reflect the actual degree of sensitivity.

It would seem that there are two phases to the whealing response of the skin to either scratch or intracutaneous tests. One is a somewhat evanescent reaction which is responsible for the reactions described above. The other is a more or less fixed or less flexible phase of the reaction. It seems quite evident in terms of our experience that treatment should be based upon the more fixed phase of the skin whealing response. Failure to take this phenomena into consideration has no doubt accounted for a great number of the failures in the previous use of the method of therapy discussed in Hansel's paper.[1]

Finally, only 7.7 per cent of the patients examined in complete detail during two seasons showed no significant change in the whealing response to any of their inhalant allergies.

INHALATION OF POLLEN

The inhalation of either the primary or secondary pollens may modify the whealing response of a given inhalant. In one case the end point of ragweed shifted from the No. 7 to the No. 2 dilution when the patient was retested four days after kochia and fourteen days after pigweed had started to pollinate. This reaction represents an increase of 3,125-fold in the whealing response. This patient gave evidence of clinical sensitivity which was parallel with this increase in skin sensitivity. It should be noted that this increase occurred before ragweed had come into the air; hence this effect was due to so-called secondary pollen, that is, pollen which did not initiate symptoms of pollinosis, yet did produce skin reactions.

In another case there was no shift to the left until after the patient had inhaled the primary pollen, ragweed, for ten days. However, this patient was also sensitive to pigweed and kochia without having evidence of pollinosis until the ragweed season.

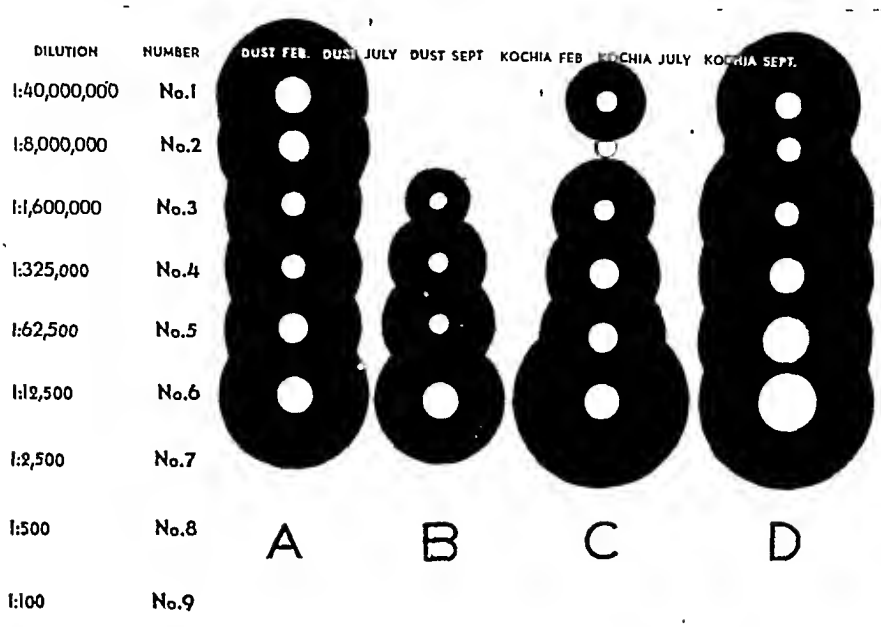

Fig. 1. A diagrammatic representation of wheaing response in relation to specific foods having a concomitant effect. (A) Ragweed tests with wheat in the diet. (B) Repetition of ragweed tests on the fifth day after elimination of wheat. (C) Reaction to ragweed when oysters had not been used for days. (D) Response to ragweed sixteen hours after ingestion of oysters, which produced both hay fever and asthma during ragweed season.

In another patient sensitive to elm pollen there was a shift of the end point from the No. 9 to the No. 7 dilution, one week after the start of elm pollination.

In connection with this shift to the left of the end point in the pollen season, emphasis should be placed on the fact that there are not just a few, but a good number of patients who have a positive skin test to a specific pollen in the pollinating season only. Therefore, if there are pollen groups in the patient's community to which the patient did not react out of season, the patient should not be assured that he is not sensitive to these inhalants. Should a patient have a recurrence of hay-fever symptoms in spite of treatment, it is necessary to recheck with those pollens which are airborne at that time and which did not give a reaction in preseasonal testing.

In one case a patient was tested on June 28 with pigweed and kochia as well as all other pollen groups in our area. Both of these tests gave only a 5 mm. wheal on the No. 9 dilution. Two weeks after the onset of pigweed pollination he reported the recurrence of hay fever which concurred with the onset of pigweed hay fever in known cases of this allergy.

A recheck of the No. 8 and the No. 9 solutions produced a reaction of 15-55 and 17-60, respectively. In many of these cases the maximum reaction is only a 7-25 response on the No. 9 dilution.

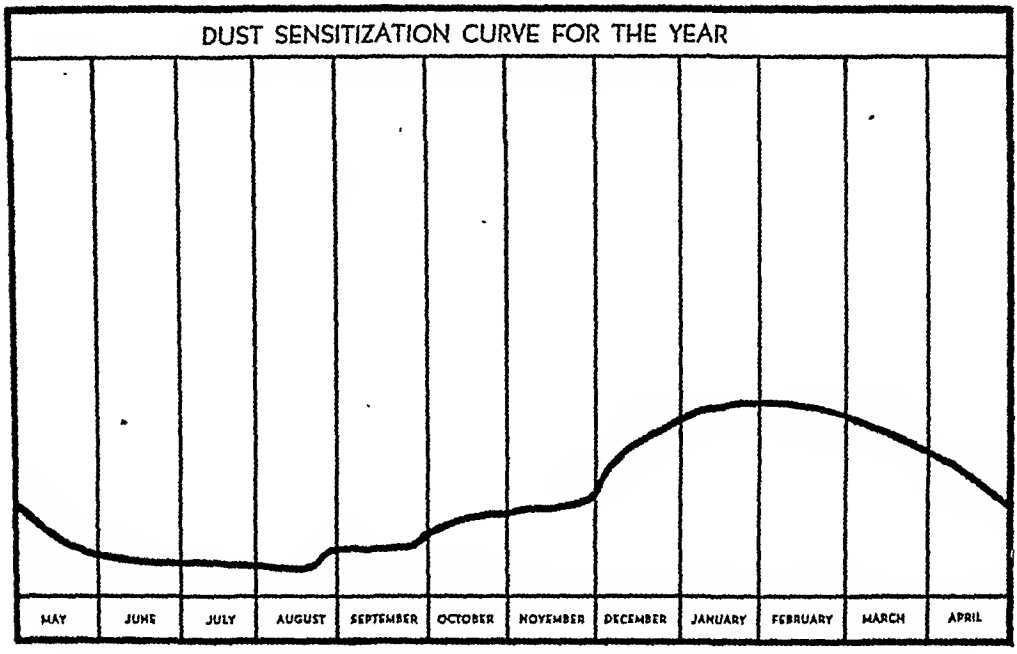

Fig. 2. Dust sensitization curve for the year, as determined by the occurrence of the end point of reaction in a series of patients. Abrupt increases occur with pollination of short ragweed and the advent of cold weather; progressive increases occur after the cold season to the peak of the year, in the last of January or early February.

THE EFFECT OF CONCOMITANT FOOD ALLERGIES

The ingestion of foods having a concomitant effect will do two things: first, they often make reactions erratic, and second, they often increase the whealing response. Figure 1, A is a diagrammatic outline of the response to ragweed with wheat in the diet. In Figure 1, B the response to ragweed is shown when the tests were repeated four days after the elimination of wheat.

In another patient with a concomitant reaction to oysters, tests were made when they had not been used for weeks. The reaction is shown in Figure 1, C. When the tests were repeated sixteen hours after eating oysters, the response had changed to that shown in Figure 1, D.

FACTORS INFLUENCING DUST SENSITIVITY

The seasonal variation in the degree of sensitivity to house dust is depicted in Figure 2. This has been determined by establishing the end point of reaction at different seasons of the year in a large series of patients.

It will be noted that the low point of sensitivity occurred during the summer months. There is an increase at the end of August with the advent of short ragweed pollen. Again, there is a more definite increase

with the first cool days in late September. This increase will occur in some patients only two or three days after it is cold enough for houses to be closed and furnaces turned on. There then follows a

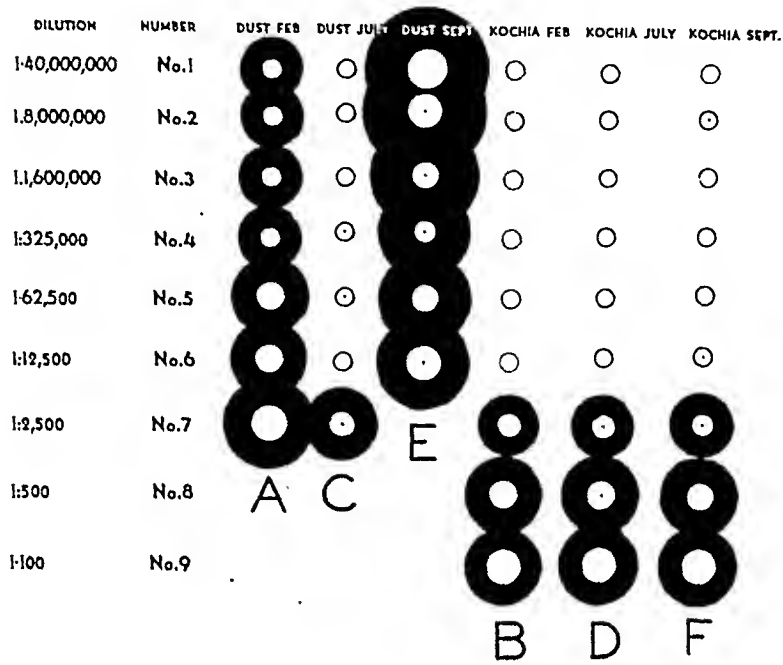

Fig. 3. Dust and kochia reactions in different seasons. (A) Dust, and (B) kochia, in February before treatment. (C) and (D) Dust and kochia a few days after start of kochia pollination. (E) and (F) Dust and kochia two weeks after start of short ragweed pollination. Note that the kochia end point did not change in any season, while dust did, and the recurrence of symptoms coincided with advent of these two pollen seasons.

gradual increase in sensitivity until the third week of January, which is the peak of the year. There is, however, a significant change early in December. This is the time when many patients have dust symptoms in spite of treatment. The most logical explanation is that these patients have sufficient discrepancy between their dose and their degree of sensitivity at this time so as to make therapy ineffective. It has been found that this seasonal breakdown is more dramatic in some years than others.

Since therapy should be in terms of existing sensitivity, it is necessary to retest dust cases at such times so as to precede a clinical breakdown in therapy. It has been found very beneficial to do this in all dust cases during the first week of December, or sooner if the patient shows evidence of therapeutic failure.

There is another phase of dust sensitivity which is of particular importance in patients with pollinosis. In Figure 3, A and B indicate the end points to dust and kochia in February. Dust and pollen therapy was effective until the first day of kochia pollination. A retest of the patient at that time is shown in Figure 3, C and D. When the dust dose was ad-

justed in terms of current sensitivity, the patient again had relief. It should be noted that the kochia and ragweed end points have not changed.

After short ragweed came into the air, the patient had a recurrence of

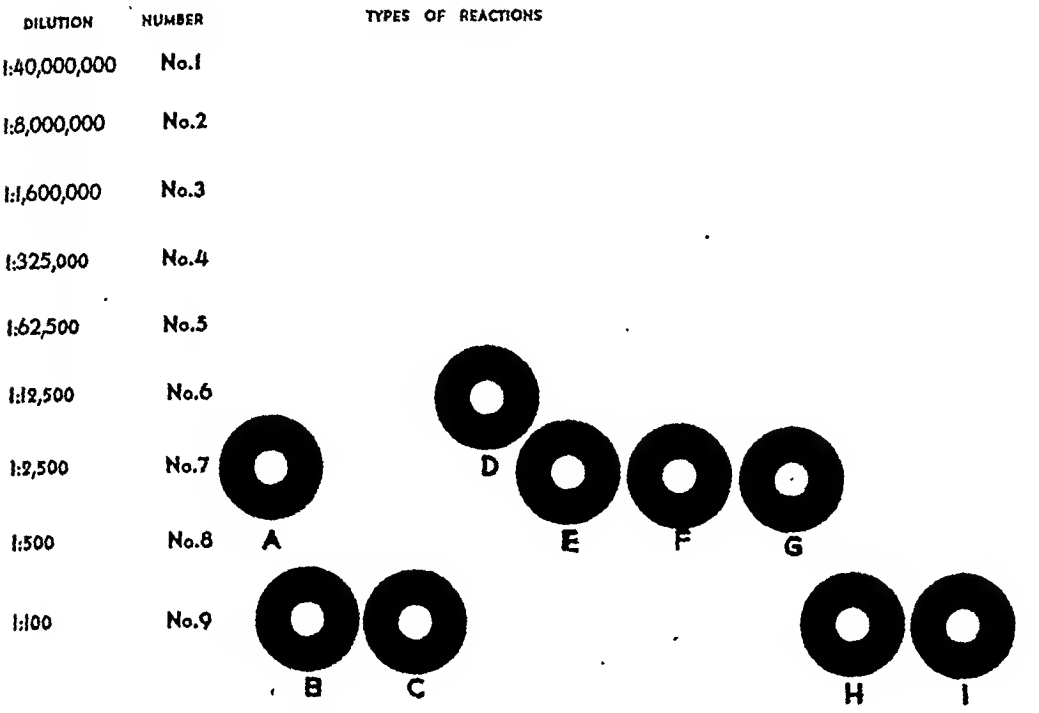

Fig. 4. End point of reaction to dust (A), elm (B), and grass (C), before treatment and before elm pollination. (D) Dust end point in elm season. (E) and (F) Elm and grass, respectively. (G) Dust end point in grass season. (H) and (I) The elm and grass end points.

symptoms, and a retest was made on September 10. This is shown in Figure 3, E and F. One may note that the dust sensitivity has increased, but kochia and ragweed have not changed. Therapy, in terms of current dust sensitivity, again relieved the patient. The influence of dust sensitivity in connection with the pollen seasons has been observed in a good number of patients who are sensitive to dust.

THE INFLUENCE OF TREE POLLEN ON WHEALING

Tree pollen is very prone to affect the whealing response, not only of its specific tests but of other inhalant groups. In Figure 4, A, B and C show the results of testing dust, elm and grass on January 25.

The patient received thirteen days of complete relief of asthma with a multiple of 50 on dust. This dose was repeated three days after elm started to pollinate, with no certain effect, but it might have increased his symptoms. The tests were repeated, and it was found that the end point of dust was now on No. 6, as shown in Figure 4, D, E and F. It may be noted that elm, grass and dust have all shifted to the left. He was again relieved when the dosage was adjusted in terms of current sensitivity. On the first day of grass pollination his symptoms recurred, when he was

tested again, with the results shown in Figure 4, G, H and I. It will be seen that dust, elm and grass have all gone back to their original end points.

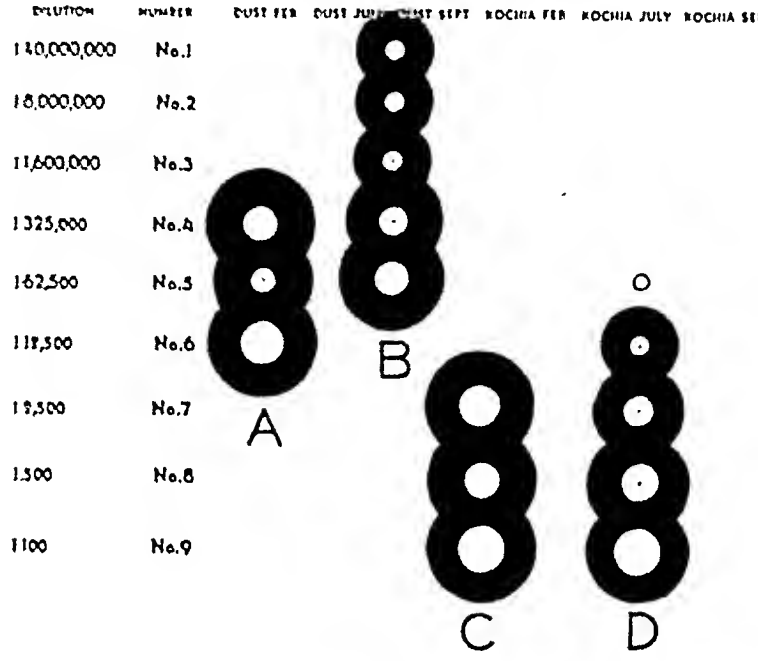

FIG. 5. Effect of overdosage or too strong initial test dose. (A) Overdosage of silk case with initial tests too strong. (B) Same tests applied four hours later, beginning with weak dose and advancing. (C) Testing with dust, with first dilution too strong. (D) Repetition of tests, beginning with weaker dose and increasing.

Tree pollen is particularly liable to cause these changes or to produce synergistic local reactions, misleading one in estimating the correct dose.

THE EFFECT OF OVERDOSAGE OR NONTREATMENT

Either overdosage or nontreatment are clinically the same as far as the patient's response is concerned. In Figure 5, A, the result of a silk titration is shown in a patient who had been overdosed. The tests were below the amount of the dose regularly given. Yet, it will be noted that the first test produced a 12-45 reaction, the second only an 8-45, and the third a 13-45.

In Figure 5, B, the results are shown of testing when the initial test was well below the end point and advanced to demonstrate progressive whealing. The significance of this second response was attested by the fact that the patient obtained ten days of relief with a multiple of 50 of this end point.

THE EFFECT OF EXCESSIVE INITIAL TEST DOSE

An excessive initial test dose is an overdose in terms of whealing response and relief of symptoms. In Figure 5, C are the results of applying the No. 7, the No. 8 and the No. 9 dust tests. It will be noted that these wheals are 11–, 8– and 12–, respectively. It can be stated almost as a rule that if the initial test dose is capable of producing a 10 mm. wheal or more, the next stronger dilution will give a lesser response and then increases will occur. When such results are obtained, one should repeat the tests starting below the level of reaction and advancing to the end point. The results of this technique for this case are shown in Figure 5, D.

It is imperative, if one wishes to establish the true end point of reaction and the actual whealing response, that tests should begin below *the dilution producing any response.*

SUMMARY

The whealing response of the skin may be reduced either rapidly or slowly by treatment. It may increase with the inhalation of either the same antigen or a so-called secondary factor, either inhalant or food. Tree pollen is particularly prone to produce increases in degree of whealing response. Excessive initial tests often give an erratic reduction in the first successive test.

When one knows the forms of whealing response to serial dilution testing and the factors which modify this, he is then prepared to apply this method of testing in clinical practice.

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REFERENCES

1. Hansel, French K.: Coseasonal intracutaneous treatment of hay fever. J. Allergy, 12:457, 1941.
2. Rinkel, Herbert J.: Inhalant allergy. I. The whealing response of the skin to serial dilution testing. Ann. Allergy, 7:631, 1949.

PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY AND STABILITY DURING NEBULIZATION

(Continued from Page 618)

by oxygen, is comparatively stable, provided sufficiently high concentrations are employed. Suggestions for the clinical application of these results are provided which demonstrate how time of therapy may be shortened, with a marked increase of the material delivered by the nebulizer.

REFERENCES

1. Abramson, H. A.: Ann. Allergy, 4:440, 1946.
2. Abramson, H. A.: Federation Proc., 6: (March) 1947.
3. Abramson, H. A., and Demerec, M.: J. Allergy, 16:184, 1945.

INHALANT ALLERGY

III. The Coseasonal Application of Serial Dilution Testing (Titration)

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THIS TECHNIQUE was presented in part before the Southwest Forum of Allergy at Houston, Texas, in 1946, by Whitney Boggs, Michael Brodkey, Fannie Lou Leney and the author.[2] Since that time there has been considerable improvement in both the fundamental knowledge and the clinical application. This communication presents the method as currently employed by a number of allergists.

PHYSICAL FACILITIES

The physical facilities are important. I use a special table mounted on casters so that all equipment can be moved from room to room. It has a stainless steel holder for the syringes along the back side, with the rinse solutions behind and slightly below the tops of the syringes.

The rinse solutions are as follows: (1) Two per cent salt and 1 per cent sodium bicarbonate with 0.4 per cent phenol. This is colored with a drop of aqueous saffron. (2) Seventy per cent alcohol, to which a slight trace of gentian violet is added. (3) Normal saline with 0.4 per cent phenol. This solution is not colored. The purpose of coloring solutions is to prevent mixture or error.

Syringes are rinsed following each test. Two may be held at a time, and three rinses are made in the first solution by filling the syringes to at least the 0.60 c.c. mark. Then two rinses are made in the alcohol, and finally, two rinses in the third solution. The inspirated material of Solutions 1 and 3 are disposed of in a waste bottle. The alcohol is returned to its container and is filtered daily. This technique has been found adequate in both terms of sterility and contamination of antigens.

One syringe is used for each antigen. Both the syringe and its holder are labeled. This label is gummed on and then painted over with a mixture of Dupont Household Cement and amyl acetate. Syringes are arranged from right to left to correspond to the occurrence of seasonal pollination. This is not only a matter of personal choice but has great practical value, for all of the pertinent pollen groups for any one season are grouped together.

In the application of the tests, one can work best seated, with the patient on a chair or stool about 5 inches higher than one's self. It is best to use a posture chair which swivels and is mounted on free rolling casters. The application of the five tests usually run at a time are made in thirty-five seconds when a nurse assists with syringes.

It is important to keep tension on the skin so as to make accurate in-

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sertion of the needle more certain. This will produce sharply demarcated wheals and will also give one a closer judgment of the amount injected. Originally, the exact amount to be injected was measured, but

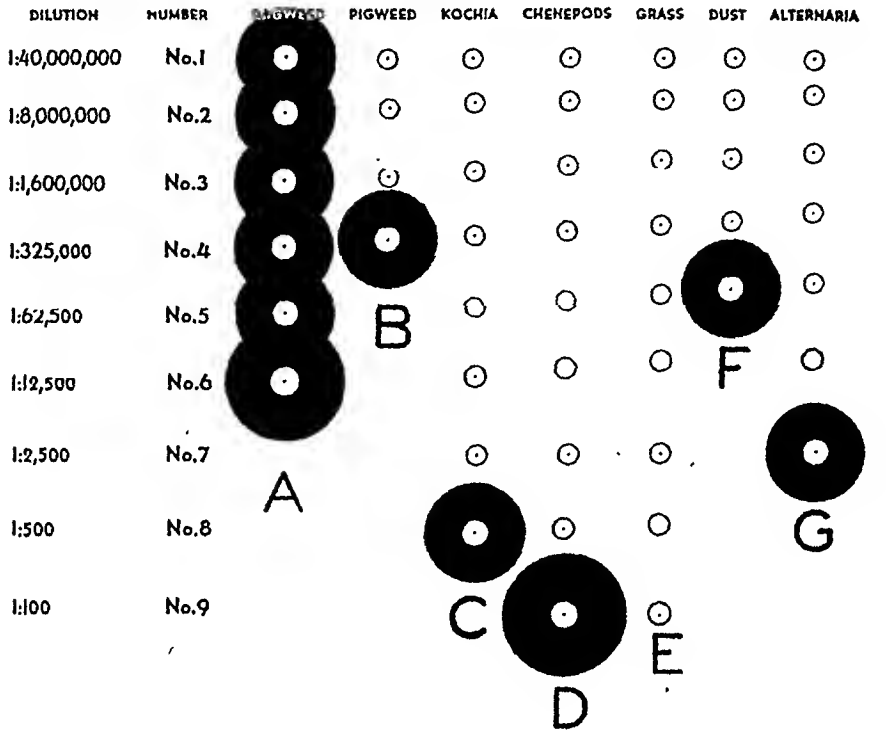

Fig. 1. Diagrammatic representation of testing and end points of reaction in coseasonal application of titration technique. (A) Linear reaction to ragweed with end point on No. 6. (B) End point to pigweed on No. 4 solution. (C) End point to kochia on No. 8 dilution. (D) End point to chenopods, which is on No. 9 dilution. (E) Grass tests which failed to react. (F) End point to dust on No. 5 solution. (G) End point of Alternaria reaction on solution No. 7.
Note that testing is discontinued after establishing the end point of a specific product.

after experience it was found possible to make a correct injection by observing the size of the wheal. This will be 4 mm. when given at the correct depth.

Four patients can be tested at a time when there is an assistant. Timing is by individual clocks, using a ten-minute interval for readings.

This method of testing may be used either preseasonally or coseasonally, but only the latter method is considered in this communication.

COSEASONAL TECHNIQUE OF TITRATION TESTING AND THERAPY

This method is, I believe, the one of choice when the patient reports for care in the season with symptoms.

Testing is started with the No. 1 solution of the entire group of inhalants which could cause the patient symptoms during the season when he suffers from pollinosis. This will vary with the areas in which the patient resides, but in our location it will include at least ragweed, pigweed, kochia, chenopods, grass, dust and Alternaria, and Hormodendrum.

Figure 1 shows the results of testing when a patient with ragweed hay fever in our locality is studied by this method.

In this illustration it will be noted that as the end point of reaction is obtained with each antigen, it is dropped from the testing. It will be seen that ragweed produces a linear erythema response. The choice of continuing tests with ragweeds is based on this fact. The occurence of a

TABLE 1. SCHEDULES AND MEASUREMENT OF MULTIPLES COMMONLY USED

Dose No.	Multiple Value of This Dose	Dilution Used End Point Dilution (For ex: No. 6)
1	15	0.15 c.c.
2	25	0.25 c.c.
3	35	0.35 c.c.
		Next Stronger Dilution (For ex: No. 7)
4	50	0.10 c.c.
5	75	0.15 c.c.
6	100	0.20 c.c.
7	150	0.30 c.c.

7-25 reaction on the No. 1 solution of ragweed may be either the end point of reaction or it may indicate the existence of a linear erythema response. Since this is the primary pollen (initiates the clinical symptoms) and the initial dose is a multiple of 15, one can safely apply the No. 2 ragweed dilution. This test is only a multiple of 5. When this is done, the occurrence of another 7-25 reveals the presence of a linear erythema response, and one can safely continue to apply the next stronger dilution every ten minutes until a wheal larger than 7-25 is produced. This occurred in this case on the No. 6 dilution. The end point of pigweed was found on the No. 4 dilution, dust on the No. 5, Alternaria on the No. 7, kochia on the No. 8, and chenopods on the No. 9 dilution, respectively. Grasses did not react.

Having established the end point of reaction to each antigenic group, therapy was started with the antigens which ordinarily could contribute to this patient's symptoms. In this case every reactor is airborne during the ragweed season; hence they all were used.

On the first treatment it has been found both safe and clinically of benefit to administer a multiple of 15 of the primary antigen, which in this case is ragweed.

The primary antigen is always kept separate, and the so-called secondary inhalants—the pigweeds, kochia, chenopods, dust and Alternaria—*may,* if one chooses, be put in a mixture as described herewith.

There is no means of determining by these or any other skin tests which dose is optimum, but in this area a multiple of 50 has been the most common satisfactory multiple. It is in keeping with this finding to make a secondary set in which all antigens appear in a multiple of 50. As can be seen in Table 1, a dose can be increased to three times this multiple without any difficulty.

In making these mixtures it is best to reduce the multiple of 50 to the smallest amount of the strongest dilution which it is feasible to measure.

The end point dilution, the dose which is a multiple of 50, and the amount and dilution to be used in the making of the secondary set are all shown in Table II. Attention is called to the fact that with chenopods where the end point is on the No. 9 dilution, the multiple is not more than 20, since this has been found best in this type of reaction. The total amount of this dose, when expressed in the smallest amount of the strongest solution

TABLE II

Antigen	End Point Dilution	Amount and Dilution Equal to Required Multiple for Antigen		Volume Used in Set
Pigweed	4	0.02 c.c.	No. 6	0.16 c.c. No. 6
Dust	5	0.02 c.c.	No. 7	0.16 c.c. No. 7
Alternaria	7	0.02 c.c.	No. 9	0.16 c.c. No. 9
Kochia	8	0.02 c.c.	No. 10	0.16 c.c. No. 10
Chenopods	9	0.04 c.c.	No. 10	0.32 c.c. No. 10
Totals		0.12 c.c.		0.96 c.c. of the mixture

feasible to measure, is 0.12 c.c. This figure is important since it represents the volume of the 1:5 dilution of this mixture which is a guide to the beginning dose of the secondary set. The first dose is selected from the regular schedule shown in Table I, which is just below this amount, and then one advances through the two dilutions according to the posted schedule of doses. For instance, the first dose less than 0.12 c.c. is 0.10 c.c. Therefore one starts with 0.10 c.c. of the 1:5 dilution of this secondary set, which is being made especially for this patient. If the amount had been 0.18 c.c., one would start with 0.15 c.c. of the 1:5 dilution.

As the various amounts indicated in the right-hand column in Table II are measured out, they are placed in a common vial which is labeled the patient's concentrate vial. Multiplying the reduced dose by 8 gives sufficient quantity of material to make a 1:5 dilution and also to advance the dose in the concentrate dilution to its maximum amount, or even more if needed.

On the second treatment one administers a multiple of 25 of the primary antigen and a quantity of the 1:5 dilution of secondary set which is computed as described above. These are given together, since there is no local reaction as a rule and nothing is to be gained by giving the patient two injections. Therapy is advanced according to the schedule given in Table I and repeated as the dose wears off, guiding all features by the clinical response. The rate of increase may be subject to individual variation as seems best in each case, but deviations from this schedule have seldom been of benefit in the respiratory allergies, unless other factors are active. This will be discussed later.

It should be noted that one may measure the same multiple by using different amounts of two different solutions, but it has been found best to have the volume of the injection around 0.50 c.c., a point which Hansel[1] first made.

It is highly important to estimate rapid change in whealing response to antigens, particularly the primary one. In one case it was found that

the end point moved from the No. 6 to the No. 7 dilution after the first treatment, which was a multiple of 15 and gave one and a half days of relief. Therefore, the second dose, instead of being 0.25 c.c. of the No.

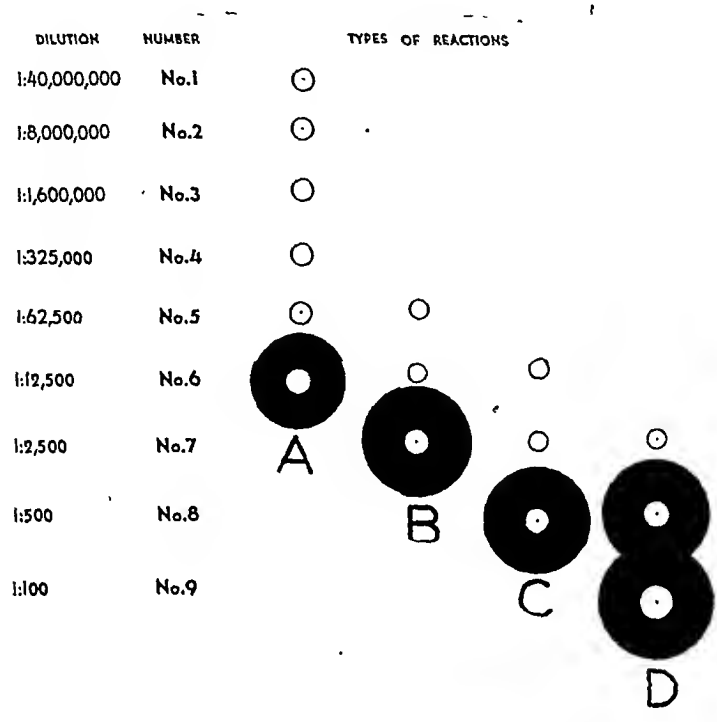

Fig. 2. Change in the end point of reaction as the result of treatment (A) Test with ragweed before treatment. (B) Testing following first therapeutic dose of ragweed. (C) End point after second ragweed treatment. (D) End point after third and successive treatments.
The importance of the shifting of the end point of reaction is depicted in this case, which if undiagnosed would lead to failure of coseasonal treatment.

6, was 0.15 c.c. of the No. 7 dilution. On the third visit the end point had moved to the No. 8 dilution, and then 0.15 c.c. of the No. 8 was given; while on the fourth visit there was no change in the end point, and then 0.25 c.c. was given, which is the second dose of the primary antigen.

In repeating these tests, one should limit his tests to a range that is less than the expected therapeutic dose. For instance, on the second visit a dose of 0.25 c.c. of the No. 6 dilution was in order. This was equal to 0.05 c.c. of the No. 7 and to 0.01 c.c. of the No. 8 dilution. Therefore, it would have consumed more than the correct second dose to have applied tests with Nos. 6, 7 and 8 solutions. For this reason the Nos. 5, 6 and 7 dilutions were used. It should be borne in mind that some of these patients increase in sensitivity with treatment; therefore, one ordinarily tests with three dilutions: one weaker than the last end point, the one giving the previous end point, and one solution stronger. The results of such testing are shown in Figure 2.

SELECTION OF ANTIGENS

It might be argued that if a patient does not have hay fever except in the ragweed season that he need only be treated with the ragweed pollen. This has not proven to be the best procedure in our area. It has been found repeatedly that treatment with a single antigen may be very effective the first year, but in successive years it has been necessary, with but few exceptions, to add the other products to which the patient is sensitive and which are in the air during his seasonal symptoms. It becomes increasingly difficult to define with accuracy what is or is not a secondary pollen. Furthermore, several of these pollens reach their peak of pollination in the ragweed season, and one should not assign all these cases to ragweed without very careful study.

It has been our custom to adequately test and treat these patients. When treatment is started with the primary antigen and the secondary mixture, one should continue to use them together, or always separate (i.e. on different days), but one should not change the schedule or omit one for a while. In some cases there appears to be a synergistic effect between certain pollens, and this effect cannot be gauged accurately if some doses are given alone. Again, there are certain individuals who cannot take the necessary dose, as determined either by titration or clinical results, until the primary and secondary products are separated. This is particularly true of tree pollen and dust injections.

ERRORS IN COSEASONAL TREATMENT

One must always be alert for the possibility of error in applying coseasonal therapeutic measures. The most important of these is a shift of the end point. It has proven to be of great help to repeat tests to establish the stabilized end point. This has never been found to exceed three times. It only requires three tests and one minute of time to apply them, a waiting time of ten minutes and a few seconds to read the tests.

The next most common error is overdosage, which is done by repeating and increasing the dose according to a fixed schedule when the patient does not get relief with a certain dose. If there is no definite relief with a multiple of 35, one should find out immediately what is wrong. I have never obtained relief with an increased dose if there was none with a multiple of 35, unless some other phase of treatment was corrected.

The third most frequent cause for failure is the attempt to build the dose to the point where the patient is getting a week's relief, simply because some other patient had been advanced successfully to that dose. I have had patients whose maximum period of relief was three days, others three weeks, with the same multiple. Patients whose end points are in the No. 1 to No. 4 dilutions are not likely to be given a full week's relief, yet those reacting on the No. 8 to No. 9 solutions are often able to go ten days in season, some two weeks and a few even three weeks.

In advancing doses from a multiple of 15 to 150 by the schedule given

in this paper, one must keep in mind that if all other causes have been evaluated, that failure to obtain a period of relief is the earliest evidence of overdosage. The earliest evidence of overdosage is not a constitutional reaction but the continuation of symptoms following a therapeutic dose.

Finally, the causes for failure are those of dietary complications. During the past three seasons I have kept a hay-fever patient in my home so that I might more fully evaluate what happens to these treated patients. It has been found that he obtained relief, *proportionately to the correctness of his diet,* when *all* inhalants were evaluated by titration. However, he was not relieved, even by diet, until he was treated for silk sensitization and for house dust allergy. He suffered severe limbic conjunctivitis with intolerable pruritus until his dust dose was adjusted.

CONCLUSION

If in the coseasonal application of titration technique and therapy one fails to get the desired relief, he should re-evaluate the degree of the sensitizations. If he is in doubt as to the dosage, begin again with a multiple of 15 and advance the dose. If the end point is on the No. 9 dilution, it might be well to start with a multiple of 5, although this is only occasionally of benefit. If this is done without benefit, then it would be logical to look for complicating sensitizations, first in foods and then in rare inhalants.

The presence or absence of limbic conjunctivitis is an important differential point between inhalants and foods causing a continuation of symptoms, it being present with the inhalants.

Titration does not give one all the answers to the problem of correct dosage, but it comes nearer to doing this than any other one procedure. It is the purpose of this method of testing to give one the best beginning dose, not to establish what the maximum optimum dose will be.

This method of testing, accurately applied, enables a physician to start treatment and accomplish results with patients having symptoms in season and to do so without danger of causing reactions. I have not had one single case of reaction from coseasonal testing with the method outlined here during the past eight years.

Finally, the average best multiple in any area may differ from what has proven to be best in my locale. Therefore, each user must ascertain his own optimum multiple for specific therapy in his geographical area.

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REFERENCES

1. Hansel, French K.: Coseasonal intracutaneous treatment of hay fever. J. Allergy, 12:457, 1941.
2. Rinkel, Herbert J.; Boggs, W.; Brodkey, M., and Leney, Fannie Lou: Round table on pollinosis. Presented at the Southwest Allergy Forum, Houston, Texas, April 4, 1946. (Unpublished.)

THE TOPICAL APPLICATION OF THEPHORIN

A Study of the Frequency of Eczematous Sensitization

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SINCE Forneau[2] and his French associates developed the first of the so-called antihistaminics or histamine antagonists, numerous compounds have been evolved which have a clinical effectiveness without prohibitive side effects. The fact that the oral administration of these medications is of value in the treatment of allergic dermatoses led to the hope that their topical application might be of additional help. Within the past few years there have been innumerable articles dealing with the subject, and it is not within the scope of this paper to review them. As is well known, there are several antihistaminic agents available for topical application.

Thephorin, the drug used in this investigation, differs chemically from the ethylenediamine derivatives (Antergan, Neo-Antergan, and Pyribenzamine) and the closely related diphenylhydramine compounds (Benadryl and Hydrallin). Thephorin base is a brand of phenindamine which is a polycyclicamine. The oral forms of the drug, syrup and tablet, contain the hydrogen tartrate salt of the Thephorin base which is also used in the ointment. The formula for the Thephorin base is 2-methyl-9 phenyltetrahydro-1-pyridindene. In this study an attempt was made to determine the incidence of eczematous sensitization in patients who had used Thephorin ointment for varying periods of time.

Wooldridge and Joseph[10] (August, 1948) reported the results of the use of Thephorin in the treatment of disseminated neurodermatitis. Their patients were treated with the syrup and tablets orally in addition to the topical use of 5 per cent Thephorin in a carbowax vehicle. Twenty-one patients were treated with both local and oral medications, and two patients received only the ointment. The period of treatment varied from one to seven weeks. Only one of the twenty-three patients became worse, although in this instance patch tests were negative.

Laymon and Schmid[1] (November-December, 1948) investigated changes in the subjective and objective signs in common dermatoses which could be obtained by the application of 5 per cent Thephorin incorporated in carbowax 1500.* Sixty per cent of the fifty-eight cases which were treated with Thephorin ointment were circumscribed neurodermatitis. The duration of treatment varied from three days to three months. Forty-four per cent were treated one week or less; an additional 21.5 per cent, from one to two weeks, and 34.5 per cent, from periods varying from two to twelve weeks. Approximately 12 per cent of the eruptions

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*Supplied by Dr. M. J. Schiffrin of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

became worse following the use of the ointment. In only one patient, however, whose eruption flared following the use of Thephorin ointment, was a patch test performed, which was negative at forty-eight hours. Thus in this group of thirty-four patients eczematous sensitization could be suspected in about 12 per cent, although it was not proved because no patch tests were performed.

There were nine patients with disseminated neurodermatitis (atopic dermatitis). Forty-four per cent of them were objectively worse following the use of the ointment. One patient obtained symptomatic relief for one month, following which she flared and presented a positive patch test to the preparation. No other patch tests were done.

The next group was made up of seven patients who presented eczematous eruptions which could not be classified. None of them became worse following the application of Thephorin ointment, and no patch tests were performed. The Thephorin ointment was also used topically in a group of miscellaneous dermatoses, including two cases of lichen planus, one of psoriasis, one of stasis dermatitis, one of dermatophytosis of the feet and ankles, one of generalized idiopathic pruritus and one of erythematosquamous seborrheic dermatitis of the ear canals. The latter patient obtained temporary objective and subjective improvement but flared six weeks after she had been using the ointment. A positive patch test was obtained. These observations proved that the topical use of Thephorin produced eczematous sensitization in two of fifty-eight patients (approximately 3 per cent). However, since patch tests were not performed in all patients whose eruptions flared, the frequency of eczematous sensitization could theoretically have been much higher.

Madden[6] also attempted to evaluate Thephorin ointment for the relief of itching in 141 cases of varied cutaneous disorders. In this study the cases were selected, and only those eruptions were chosen where it was thought proper to use an ointment. The lesions were generally dry. Vesicular, pustular, secondarily infected or weeping eruptions or those accompanied by cellulitis, lymphangitis, acute lymphadenitis or fever were excluded. In seven cases (5 per cent) the eruptions were aggravated, although no patch tests were performed. For this reason it is impossible to judge the incidence of eczematous sensitization, although one may assume that it was not greater than 5 per cent.

Shelmire[7] (November, 1948) observed six instances of contact-type sensitization among 455 persons, an incidence of 1.31 per cent. He felt that this was a low sensitizing index, especially if one considered that the ointment was used by large number of patients over a comparatively long period of time and that considerable quantities of the preparation were applied.

Sulzberger and Baer[8] recently stated that it is unfortunate that the usefulness of the antihistaminics is impaired by the paradoxic findings that some of them are not always antiallergic but sometimes even rela-

tively strong sensitizers. These authors mentioned that they had seen allergic eczematous contact-type dermatitis from several antihistaminics, including Thephorin and Pyribenzamine, as well as drug eruptions of various kinds from most members of the so-called antihistaminic series.

TABLE I

Types of Dermatoses	No. of Patients	Per Cent
Pruritus (anal and vulvar)	34	10.48
Neurodermatitis (circumscribed)	97	29.92
Lupus erythematosus (chronic discoid)	1	0.30
Dermatophytosis	4	1.23
Contact dermatitis	35	10.80
Atopic dermatitis	24	7.42
Dermatitis unclassified	6	1.85
Pruritus senile	29	8.96
Psoriasis vulgaris	14	4.32
Bites, insect	10	3.08
Tinea glabrosa	1	0.30
Seborrheic dermatitis	16	4.94
Stasis dermatitis	4	1.23
Urticaria	5	1.58
Lichen planus	5	1.58
Dermatitis medicamentosa	1	0.30
Lichen sclerosus et atrophicus	1	0.30
Pityriasis rosea	18	5.56
Dermatitis herpetiformis	2	0.62
Dermatitis solare (acute sunburn)	2	0.62
Pruritus hiemalis	11	3.39
Rosacea	1	0.30
Folliculitis	2	0.62
Herpes zoster	1	0.30
Total	324	100.0

TABLE II

Duration of treatment	No. of patients	Per cent
Up to 7 days	53	16.25
1 to 2 weeks	122	37.75
2 to 3 weeks	40	12.35
3 to 4 weeks	36	11.11
1 to 2 months	37	11.41
2 to 3 months	20	6.18
3 to 4 months	5	1.58
4 to 5 months	4	1.23
5 to 6 months	2	0.62
6 to 7 months	1	0.30
7 to 8 months	2	0.62
8 to 9 months	1	0.30
10 months	1	0.30
Total	324	100.0

PRESENT STUDY

In this investigation, patch tests were performed on 324 patients with various dermatoses who had used Thephorin ointment for periods ranging from a week to ten months. In most of the patients three patch tests were performed, utilizing: (1) the 5 per cent standard Thephorin ointment, (2) carbowax 1500, and (3) a 2 per cent solution of the Thephorin base. The tests were removed at twenty-fours and read at forty-eight hours. The results can be best summarized in tabular form.

There were many patients whose eruptions were aggravated by the use of Thephorin ointment but in whom eczematous sensitization could not be proved by patch testing. In these patients the lesions might have flared if anything or nothing had been used. Table III summarizes those patients whose eruptions were aggravated by the use of the ointment and who

TABLE III

Sex	Age	Diagnosis	Duration of Treatment	Results of Patch Tests
1.F	41	Neurodermatitis	1 month	Ointment-positive Base-0 Solution-positive
2.M	56	Contact dermatitis	2 days	Ointment-3 + Base-0 Solution-4 +
3.F	35	Pruritus vulvae	2 weeks	Ointment-? Base-positive Solution-positive
4.F	50	Atopic dermatitis	2 months	Ointment-3 + Base-0 Solution-4 +
5.F	65	Neurodermatitis	2 weeks	Ointment-4 + Base-Not tested Solution-4 +
There were two other cases in which reactions occurred apparently as a result of sensitization to carbowax:				
1.F	33	Pruritus Ani	8 days	Ointment-positive Base-Not tested Solution-negative
2.F	36	Neurodermatitis	3½ months	Ointment-positive (erythema) Base-positive (erythema) Solution-negative

developed true eczematous sensitization as indicated by a positive patch test.

COMMENT

It would seem from an analysis of these reactions that the time element is of some importance as far as eczematous sensitization to Thephorin is concerned. All cases of sensitization developed within a period of two months, and none of the sixty-three patients who continued the use of the preparation longer than two months encountered any difficulty. It is noteworthy that every single instance of sensitization occurred in patients who had eczematous eruptions and that patients with non-eczematous eruptions such as psoriasis, lichen planus, pityriasis rosea, et cetera, encountered no difficulty whatsoever. As is well known, this holds true for sensitizations to innumerable other substances, including the sulfonamides, antibiotics, furacin and other chemicals.

As mentioned earlier, the clinical flare of an eruption does not necessarily mean the development of true eczematous sensitization. Such is the case in all types of topical therapy regardless of the agent which is being used. In this group of 324 cases, eczematous sensitization developed in approximately 1.5 per cent within a period of two months. This indicates that Thephorin is a much less potent sensitizer than several other topical medications such as the sulfonamides, penicillin and furacin. Hopkins and Lawrence,[3] for example, found that allergic cutaneous reactions appeared in 11 per cent of all patients and in 25 per cent of those with eczematous dermatitis who received penicillin topically. Sulzberger, Kanof, Baer, and Lowenberg[9] found that 19 per cent of a group of 254 experimental subjects developed dermatitis following application of the sulfonamides. Downing, Hanson and Lamb[1] noted that approximately 10 per cent of sixty-five patients treated with furacin ointment became

sensitized, while Lynch[5] noted even a higher percentage of eczematous sensitizations (15 to 25 per cent). As time goes on, and Thephorin ointment continues to be used, the percentage of sensitizations may change. While our data on 324 cases indicate that Thephorin ointment sensitizes only 1.5 per cent of individuals upon which it is used, time alone will determine its true index of sensitization.

SUMMARY

1. Patch tests were performed on 324 patients with various dermatoses who had used Thephorin ointment for periods varying from a few days to ten months.

2. Flares of the eruptions plus positive patch tests indicated eczematous sensitization in 1.5 per cent of the subjects.

REFERENCES

1. Downing, John Godwin; Hanson, Millard C., and Lamb, Marion: Use of 5-nitro-2-furaldehyde semicarbazone in dermatology. J.A.M.A., 133:229-306, (Feb.) 1947.
2. Forneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau derive due dioxane. Arch. Internat. de Pharmacodyn. et de Therap., 46:178, (Oct. 15) 1933.
3. Hopkins, J. Gardner, and Lawrence, Herbert: Penicillin therapy in pyogenic dermatoses. Am. J. M. Sc., 212:674-681, (Dec.) 1946.
4. Laymon, Carl W., and Schmid, John F.: The topical application of Thephorin in pruritic dermatoses. Ann. Allergy, 6:638-644, (Nov.-Dec.) 1948.
5. Lynch, Francis W.: Personal communication.
6. Madden, John F.: A clinical evaluation of Thephorin ointment for the relief of itching (a preliminary report). Arch. Dermat. & Syph., (in press).
7. Shelmire, Bedford: Topical treatment with Thephorin. Postgraduate Med., 4:5, (Nov.) 1948.
8. Sulzberger, M. B., and Baer, R. L.: Editorial comment, Yearbook of Dermatology and Syphilology. P. 128. Chicago: Yearbook Publishers, 1948.
9. Sulzberger, M. B.; Kanof, Abram; Baer, R. L., and Lowenberg, Clare: Sensitization by topical application of sulfonamides. J. Allergy, 18:92-103, (March) 1947.
10. Wooldridge, W. E., and Joseph, H. L.: Thephorin in the treatment of disseminated neurodermatitis. J. Invest. Dermat., 11:93, (Aug.) 1948.

INHALANT ALLERGY

(Continued from Page 630)

tests (or scratch tests under certain conditions) is to be certain as to the relation of any test with a given solution to the entire reaction. Specifically, one must be sure that a certain response, considered significant, is either the end point of reaction or has a definite relationship to it. In a subsequent communication these points will be discussed in detail.

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REFERENCE

1. Hansel, French K.: Coseasonal intracutaneous treatment of hay fever. J. Allergy, 12:457, 1941.

CORN SUGAR AS AN ALLERGEN

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RINKEL first called attention to the clinical significance of corn sensitivity, having demonstrated in an exhibit at the annual meeting of the Southern Medical Association in 1936 that corn was fourth among various foods listed in the order of the incidence of sensitivity. Since that time he has continued to emphasize the importance of sensitivity to maize and its products, finally presenting the problems of the corn-sensitive patient at the Omaha Instructional Course of the American Academy of Allergy in 1947.

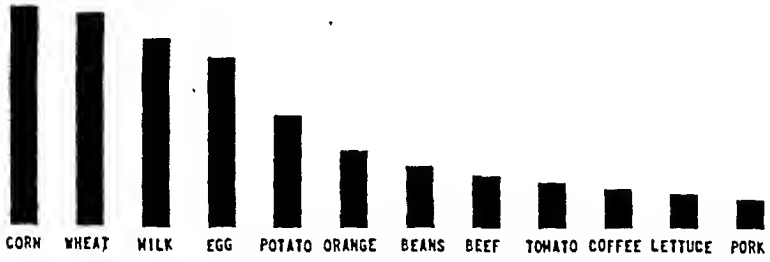

Fig. 1. The order of incidence of foods causing masked or cumulative allergic reactions. The incidence of sensitivity to corn, wheat, milk and eggs was determined from a survey of 200 consecutive cases studied for food allergy by direct methods, i.e., by means of individual food tests with those four foods and subsequent clinical follow-up. The relative incidence of sensitivity to other foods is estimated from clinical experience.

One of us (T.G.R.), in discussing another paper on the subject of food allergy at the 1946 annual meeting of the American Academy of Allergy, stated that corn sensitivity was second only to wheat as a specific cause of chronic food allergy. This statement was based on a study of eighty-five consecutive cases investigated for the presence of specific food sensitivity by means of individual food tests with wheat, corn, milk and eggs. This series has since been extended to include 200 consecutive cases studied similarly, the results of which indicate that corn sensitivity is now at least equal to that of wheat allergy and appears to be slightly greater in incidence, as illustrated in Figure 1. This study, comprising 160 adults and forty children of pediatric age, has been reported elsewhere.[5,10]

Urbach and Willheim[21] suggested the possibility of allergic reactions to sugar of corn origin in 1932. Rinkel has repeatedly stressed the importance of corn sugar in respect to handling the corn-sensitive patient for over a decade, presenting a case at the first instructional course of the American College of Allergists in 1944, which illustrated that the inges-

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tion of corn sugar in bacon caused headaches,[16] and that corn sugar in candy, gum, ices, commercially canned fruit and pharmaceutical preparations resulted in allergic reactions in individuals sensitive to corn. Coca[1] also referred to the fact that an individual sensitive to corn must avoid corn sugar. The first comprehensive experimental study of this problem was made by Ratner and Gruehl[11] in 1935. They determined that corn sugar syrup and crystalline sugar, derived from the hydrolysis of corn starch, were non-anaphylactogenic for guinea pigs, and, presumably from this data, concluded that these products were not important in clinical allergy. At least, other evidence, such as experimental feeding tests with corn products or even skin tests with extracts of corn, was not cited in reaching this conclusion.

Although we have been able to confirm their anaphylactic studies in guinea pigs, we are not in agreement with their deductions regarding the clinical significance of corn sensitivity. This presentation will deal, primarily, with the clinical evidence in support of the thesis that sugars of corn origin are allergenic in many highly corn-sensitive individuals.

It should be pointed out at the onset that our opinion on the subject of corn sensitivity has undergone considerable change during the course of the past five years. Interest in the detection of clinical allergic reactions to corn has developed as we gradually learned the sources of corn in the diet and thus became able to instruct our patients more adequately in its specific avoidance. We were aided in the beginning by having access to the list of corn sources compiled over a previous period of several years by Rinkel.[12] However, we were still unable to relieve completely the symptoms of certain cases of corn sensitivity, even though they were correctly diagnosed in this respect, until we had learned of the presence of corn starch employed as a sizing on the inner surface of paper food containers,[6] of the commercial practice of dusting the surfaces of certain plastic-type containers with corn starch,[6] of the use of corn starch as a diluent and excipient in many pharmaceutical preparations,[7] and of additional sources of corn sugar in other prepared foods and medications. In this connection it might be added that we have never observed a patient, even though he knows that he is corn sensitive and has attempted to avoid its ingestion, who has been able to remove corn from his diet in the absence of specific instructions of *how* to do so.

The other major factor in our ability to recognize the clinical significance of this problem occurred coincidentally with the abandonment of the practice of performing skin tests with food extracts five years ago, since which time the individual food test has been employed as the major diagnostic criterion for the detection of specific food sensitivity. The present technique of this test, described by Rinkel,[11] has been confirmed by Randolph and Rawling.[9]

In an attempt to appraise the clinical importance of this question, one of us (T.G.R.) in 1944 subjected all new patients suspected of having symp-

toms due to food allergy to the deliberate experimental feeding of corn. The results of this study were impressive in respect to the true incidence of corn allergy. Since this time, all new patients and many previously studied, who had symptoms of the general type suggestive of food sensitivity, have been subjected routinely to individual food tests to determine the existence of allergy to corn.

From this experience, it is our impression that current differences of opinion in respect to the clinical significance of allergy to maize and its products is due in part to the inability of patients and clinicians to avoid its ingestion, and in part to the perpetuation of out-moded methods of specific food diagnosis. In the latter connection, we refer particularly to the mechanical performance of cutaneous and intracutaneous skin tests with food extracts and, to a lesser extent, to the continued use of certain restricted diagnostic diets which do not specifically eliminate certain corn-containing products.

In order to prepare a patient adequately for an individual food test with corn, it is essential that *all* ingested sources of corn be completely avoided for at least four days prior to experimental feeding; otherwise the masked symptoms of corn sensitivity may be perpetuated, and under such circumstances an experimental feeding may fail to produce a diagnostic clinical response. Furthermore, in keeping with the fundamental concept of masked food sensitivity developed by Rinkel,[13] the patient being tested in the absence of adequate preparation might be expected to have his chronic smoldering symptoms actually improved following a meal of corn. A case may be cited to illustrate this common error in the specific diagnosis of corn allergy:

Case 1.—M. M., a man, aged thirty-nine, had been subject to perennial allergic rhinitis and severe chronic headaches, associated with some of the symptoms of the fatigue syndrome, as originally described by Rowe[18,19,20] and recently reviewed.[3,4] An individual food test with milk was associated with the prompt development of severe headache and somnolence. When interviewed, following his test with corn, he volunteered the information that he knew that this food was not causing trouble because he felt decidedly better after eating the test-feeding than he had immediately prior to it. This type of remark, to one familiar with the method, arouses the suspicion that his preparation for the test may have been faulty. It then developed that he had been in the practice of eating a brand of bacon cured by means of a process known to have contained corn sugar and had received his last feeding of this in the morning prior to his noon test for corn sensitivity. He was then told to follow his instructions adequately (the highly corn-sensitive patient must eat only certain approved brands of bacon to be certain that all sources of corn are removed) in preparation for a second test. With this he promptly developed reactive symptoms of a severity and time sequence diagnostic of specific allergy.

The following cases will be cited to illustrate the necessity for the continued avoidance of corn sugar in order to effect relief of symptoms due to corn sensitivity:

Case 2.—L. C., a woman aged forty-eight, had been subject to the typical symptoms of the fatigue syndrome for the past seven years. In her case, these included unexplained fatigue, depression, melancholia, irritability, tachycardia, intermittent chilliness and generalized muscle aching. She had also complained of chronic soreness of her throat, postnasal discharge and intense itching of the eyelids and ear canals. Her individual food test with corn was associated with generalized abdominal discomfort, followed by acute abdominal cramps and diarrhea, with delayed symptoms during the night of the test consisting of insomnia, generalized pruritus and urticaria. The elimination of corn and other incriminated foods resulted in a striking improvement of her local and constitutional symptoms. She returned six weeks later, stating that she had had a return of her weakness and aching for the past four days. The food diary revealed that she had eaten tenderized ham in the evening meal prior to the onset of these symptoms and had also consumed it in two subsequent additional feedings immediately prior to the recurrence of her depression and melancholia. Upon inquiry, the statement of the manufacturer revealed that this brand of ham contained corn sugar. Her symptoms subsided with the omission of ham but recurred subsequently following its reintroduction to the diet. Follow-up observations revealed that she tolerated fresh pork and other recommended brands of ham which were processed without the addition of corn sugar.

Case 3.—J. R., aged four, had complained for several months of chronic coughing, recurrent "colds" and gastrointestinal symptoms which on several occasions had suggested the possibility of intestinal obstruction. Her father, a physician, had been particularly concerned with her chronic listlessness, irritability and sluggishness, more marked on certain days than on others. He had noticed that she was developing into a progressively troublesome behavior problem, meeting a characteristic description.[4]

She was found to be highly sensitive to house dust, wheat, corn and egg. With the continuation of specific dust therapy and the elimination of these foods, there has been a striking improvement in her symptoms and general behavior. For the last year she has remained an active, healthy and well-adjusted child. Coincident with starting nursery school, however, she lapsed into her former symptoms. It was then learned that the fruit juices served during mid-morning at the school were sweetened with corn sugar. Her symptoms again subsided with the cessation of these drinks and recurred when they were returned to her diet, although she was not clinically sensitive to any of the fruits as such. On another occasion similar symptoms were reproduced when she was served maple syrup, subsequently learned to have been adulterated with corn syrup.

Several acute allergic reactions have been observed to follow the ingestion of various types of corn sugar; illustrative examples are given in the following cases:

Case 4.—E. M., a physician's wife, aged twenty-two, gave a history of intermittent asthma since childhood, acute gastrointestinal upsets beginning at the age of fifteen and the onset of perennial allergic rhinitis and chronic fatigue at the age of nineteen. Her fatigue and weakness were accentuated intermittently in association with periods of tender, swollen cervical glands, as previously described,[8] and particularly with bouts of acute rhinitis occurring in the middle and late summer months prior to her first visit in May, 1946.

Specific treatment for her house dust sensitivity failed to afford satisfactory relief of her symptoms. Food diary evidence revealed attacks of sneezing, pruritus and urticaria following meals containing corn on the cob. An individual food test

with corn (using corn meal gruel only) was followed by abdominal cramps, generalized itching, marked fatigue and a recurrence of her tender, swollen, anterior cervical lymph glands. The complete elimination of corn products and the continuation of dust therapy afforded complete relief of symptoms.

After several weeks of corn avoidance, she reported an inexplicable attack of severe sneezing and nasal obstruction which started during the evening meal and continued all night. She was slightly nauseated the following morning and remained exceedingly tired throughout that day. She was at a loss to explain this attack because she had not eaten any food previously known to have caused symptoms. Neither were there any clues in her food diary to explain this acute reaction. After a prolonged period of questioning, it finally came out that corn on the cob had been served to other members of the family and that it had been cooked by the patient. The same meal was repeated five days later and produced an identical type of reaction, but the same menu with the absence of corn was tolerated. Subsequently it has been shown on repeated occasions that the inhalation of the fumes of cooking corn (osmyls) will produce acute allergic reactions in this individual.

Early in the course of this patient's studies, an attempt was made to determine the effect of the ingestion of dextrose. On the fifth day following an acute corn reaction, this food having been absolutely eliminated in the interim, she was fed 150 grams of U.S.P. dextrose (C.P.), dissolved in 300 c.c. of tap water. Within five minutes she drank an additional 200 c.c. of water. Fifteen minutes later she developed nausea and complained of feeling tense and "shaky," and at thirty minutes she first noticed abdominal cramps. An hour after the first dose, an additional fifty grams of dextrose was administered in 150 c.c. of water. Her nausea was accentuated within ten minutes, followed by vomiting at twenty minutes. One hour after the second feeding she developed mild rhinitis and sneezing, which persisted for a half hour, and a severe frontal headache which remained troublesome for three hours. She remained unusually tired for the following day, during which time she continued to have occasional abdominal cramps.

The question may be raised, which cannot be denied, that the amount of glucose ingested would have made any person sick. It should be pointed out, however, that the amount of the first dose was approximately that given in routine glucose tolerance tests and that she developed symptoms prior to the second feeding. Furthermore, the symptomatology which she exhibited is typical of that of the allergy patient and identical symptoms have been produced in her following the ingestion of other forms of corn.

During the past two years this patient has been very helpful in her ability to detect the presence of corn sugar in unlabeled processed foods. For instance, she has been able to determine its presence in certain brands of canned fruits and vegetables, a particular brand of Graham crackers, waffle syrup (alleged to have been maple but subsequently found to have been adulterated with corn syrup) and other prepared foods not suspected of containing corn at the time they were eaten. It is from patients of this type and degree of sensitivity that we have been able to determine the sources of corn in the diet.

Case 5.—M. McW., aged thirty-seven, had been subject to severe perennial allergic rhinitis with intermittent complete nasal obstruction and marked itching of her nose for five years, and frequent headaches and occasional urticaria for a year prior to her first visit. Tomatoes were suspected of causing hives, but no other foods were under suspicion except corn, which caused gastrointestinal distress, presumably on the basis of its "roughage."

House dust hyposensitization resulted in only partial improvement of her rhinitis. There was no other evidence of inhalant sensitivity.

Sixty cubic centimeters of corn syrup (stated by the manufacturer to be free of

all other agents except corn syrup) were ingested, while fasting, at a time when the patient was symptom-free after four days of complete corn avoidance. She developed a blinding headache ten minutes later, followed immediately by marked dizziness. The patient was obviously acutely ill and too dizzy to walk across the floor. She was helped to her feet but was unable to stand with her eyes closed in attempting to perform a Romberg test. She was aided in returning to her home. Dizziness, headache and extreme fatigue persisted for two days.

She was also found clinically hypersensitive to wheat and onion. With the continuation of dust avoidance and specific therapy and the complete elimination of corn and other incompatible foods, she has had complete relief of symptoms during the past two years except when she would inadvertently encounter sources of corn. On repeated occasions the ingestion of corn syrup or corn sugar (dextrose or glucose) would be followed by the recurrence of allergic symptoms.

Case 6.—M. F., assistant hospital superintendent of nurses, aged thirty-seven, had been subject to typical atopic dermatitis until the age of twenty-seven, intermittent bronchial asthma and perennial allergic rhinitis for five years, and periodic frontal headaches associated with extreme fatigue since childhood. In the year prior to her first visit in July, 1945, she had complained of increasing frequency and severity of headaches which were associated with continuous fatigue. Acute indigestion with heartburn and bloating occurred after certain meals. Chicken was suspected of causing this reaction, but it only accounted for a few of her attacks.

There was no history or skin test evidence of inhalant sensitivity. An individual food test with canned corn was followed by tenseness and "nervousness" at forty-five minutes. A second feeding an hour later was followed by a severe headache, dizziness and mental confusion. Residual fatigue persisted for twenty-four hours.

Five days later, a clinical test with corn syrup was performed. She had completely avoided corn and other known allergens for four days prior to the test, and was symptom-free and fasting when fed 60 c.c. of Karo syrup with as much water as desired. Forty minutes later she complained of drowsiness but developed no other symptoms. She was fed half the amount an hour after the first dose. Ten minutes later she noticed an increase in her somnolence associated with the desire to sneeze; these symptoms continued for the remainder of the day, and three hours after the last feeding, they became associated with increasing nausea. Four and one-half hours after the second feeding she complained of marked weakness, trembling and shaking. Seven hours after the second feeding (having had no other foods or medications in the interval) she developed severe generalized abdominal tenderness, distention and cramps, followed by acute nausea. Shortly thereafter she passed a liquid stool which was followed in the next five hours by eight to ten additional diarrheic stools, which contained much mucus, the last three containing fresh blood. Severe nausea and griping abdominal pains persisted through the night. The following morning she felt better except for extreme fatigue. However, at 8:00 p.m. the second day she developed chills and a temperature elevation of 101° F., followed immediately by a severe attack of asthma which necessitated her admission to the hospital. All food ingested since her corn test and prior to her asthma had been shown to be compatible as a result of subsequent observation. There was no other apparent cause of the clinical reaction described except the ingestion of corn syrup.

She was also shown to be clinically sensitive to chicken, peas, and milk. With the avoidance of these foods and all sources of corn, she had no further troublesome symptoms. A year later she developed a minimal tuberculous lesion of the chest but otherwise has enjoyed the best of health except when encountering sources of corn or other incriminated foods.

TABLE I. UNSUCCESSFUL ATTEMPTS TO PRODUCE ACUTE ANAPHYLAXIS BY THE INTRAVENOUS ADMINISTRATION OF CORN SYRUP IN GUINEA PIGS IN WHICH PREVIOUS EFFORTS HAD BEEN MADE TO INDUCE CORN SENSITIVITY

	Sensitizing Procedure					Shocking Procedure			
Material Used:	A. 50% Aqueous Solution of Corn Syrup B. Saturated Solution of Corn Flour C. Corn Flour in Aluminum Hydroxide Cream					1.0 cc. 50% Aqueous Solution of Corn Syrup Injected intravenously in all cases.			
Route of Sensitizing Doses	No. of Guinea Pigs	No. of Injections	Interval in Days Between Doses	Amount Injected in cc..	Material Injected	Interval in Days After Last Injection	Acute Anaphylaxis	Questionable Anaphylactic symptoms	No Symptoms
Intraperitoneal	2	2	4	5.0	A.	19	—	—	2
	6	3	3	5.0	A.	16	—	—	4
	2	2	6	1.0	B.	16	—	—	2
Subcutaneous	2	3	3	2.0	A.	14	—	1	1
	2	1	—	1.0	B.	14	—	—	2
	3	2	6	1.0	B.	16	—	1	2
Intramuscular	4	1	—	1.0	C.	16	—	1	3
	4	2	7	1.0	C.	23	—	1	3

These patients, as well as many others observed in our practice, have been able to detect exceedingly small amounts of corn sugar or syrup as it is encountered in commercial foods. In numerous instances we first became aware that certain foods produced symptoms in our controlled corn-sensitive patients, and then determined from correspondence with the manufacturer that the foods in question actually did contain sugar of corn origin.

Other cases of corn sensitivity in children in which the accidental or intentional ingestion of corn sugar produced acute allergic symptoms have recently been reported by one of us.[4]

In view of the statement of Ratner and Gruehl[11] that corn sugar syrup and crystalline sugar derived from corn were non-anaphylactic for guinea pigs, attempts were made to sensitize twenty-five guinea pigs to various corn products, following which an intravenous injection of corn syrup was administered in an effort to produce anaphylaxis. The following materials were used as antigens: 50 per cent corn syrup in aqueous solution (ten pigs), a saturated solution of corn flour in saline (seven pigs), and corn flour suspended in aluminum hydroxide cream prepared by the method of Hektoen and Welker[2] (eight pigs). The corn syrup used in the experiments was furnished by the Corn Products Refining Company. According to their analysis, the dextrose equivalent of the undiluted syrup was between 42.5 and 44.5, the remainder of the material consisting of dextrins. The sample contained 0.037 per cent total protein, and no ammonia nitrogen was found. The varying dosages and the routes of administration of the sensitizing injections and results of the experiments are summarized in Table I.

As may be observed from this table, we were unable to induce acute

anaphylaxis in any of the test animals. The term "questionable" anaphylactic symptoms refers to rubbing of the nose and sneezing. One animal, injected intraperitoneally by repeated doses of corn syrup, developed fecal incontinence in addition. All "reactions" were transitory, and it cannot be said that they constituted true anaphylactic responses.

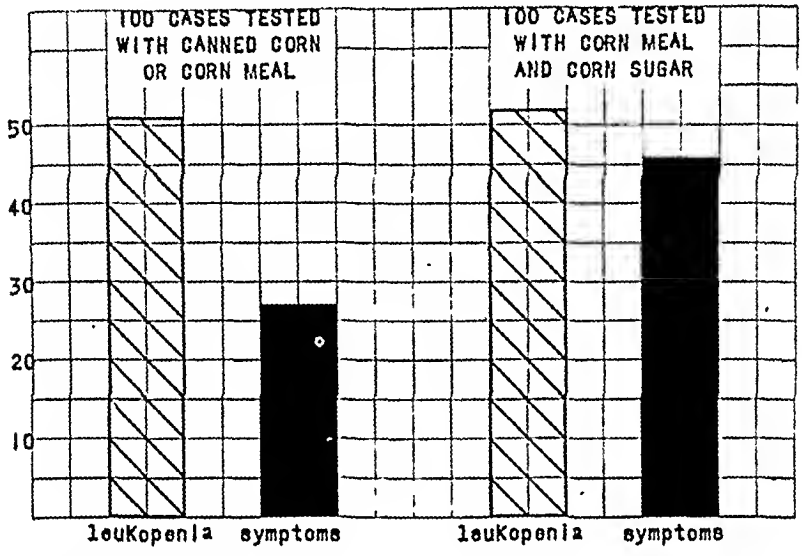

Fig. 2. The incidence of corn sensitivity as determined by individual food tests.

DISCUSSION

In view of the frequency with which acute reactions may be produced in corn-sensitive patients, following the experimental or accidental ingestion of sugar of corn origin, the reader may wonder why the allergenicity of corn sugar has not received greater emphasis. Perhaps Ratner and Gruehl's observations that corn sugar did not act as an anaphylactogen, and presumably not as an allergen, retarded the clinical recognition of the matter. However, the major factors in our failure to appreciate the problems associated with corn allergy appear to be: first, the fact that sensitivity to corn is usually a masked type of clinical response and, therefore, not readily observed either by the patient or his physician; and second, the fact that corn products are so widespread in the diet that it is difficult to eliminate them completely so as to effect clinical relief.

Rinkel[13] has shown that a patient will recover from the masked effects of a food taken frequently in the diet after a four-day period of complete avoidance. The experimental ingestion of corn sugar in the highly corn-sensitive patient, who has been receiving corn daily for several weeks before avoiding it prior to such a test, is frequently followed by a sharp and unmistakable clinical reaction.

In fact, the highly sensitive patient, otherwise controlled as far as his corn allergy is concerned, will usually react with more immediate symptoms following the ingestion of corn sugar than he will from eating corn starch,

corn as such, or corn oil. This phenomenon, also observed independently by Rinkel,[12] has been shown to exist in a series of 100 consecutive individual food tests performed by feeding cooked corn meal only, as compared with a similar group of undiagnosed patients suspected of food allergy but fed cooked corn meal plus corn sugar. The striking difference in the frequency of reactive symptoms in relation to the presence of a leukopenia of 10 per cent or greater, occurring from any previous total leukocyte count, is illustrated in Figure 2. The addition of corn sugar to the test feeding has materially increased the diagnostic accuracy of individual food tests with corn as determined by the production of objective symptoms. There appears to be no appreciable difference in the actual incidence of corn sensitivity in the two groups of cases as determined by the results of cumulative feeding and clinical follow-up. Prior to making this change in our test technique, we were disturbed by the fact that we were not encountering the same percentage of reactive symptoms in our cases of corn sensitivity under test conditions as in the cases of wheat, milk or egg sensitivity. Since making the above change in technique and learning of the additional sources of corn starch—in food containers[6] and as excipients in pharmaceuticals[7]—we have encountered about the same percentage of symptoms in the corn cases, in respect to the definition of leukopenia, as in similar tests with other foods.

In a great many corn-sensitive individuals, the chronic symptoms of corn allergy will not subside until corn sugar has been completely eliminated. This entails the avoidance not only of corn syrup but also of dextrose, glucose (including such trade name products as Cerelose, Sweetose, Dyno, Cartose, Karo and Puretose), a problem that has been rendered even more difficult by inadequate federal labeling regulations. Actually, corn sugar is used so widely in commercially sweetened products that the consumer must assume that the current designation of "sugar" may mean sugar of corn origin. At the present time, in order to avoid corn exposure, the patient must buy only recommended trade name products of certain types of commercially prepared foods. An attempt is now being made to bring a list of this type up to date; this data will be published elsewhere.[17]

The question may be raised concerning the possibility of intravenous dextrose or glucose causing reactions in corn-sensitive individuals. Although the incidence of such reactions is not known, there is no doubt that they occur, as judged by the histories of exquisitely corn-sensitive patients and a few instances where clinical reactions have been experimentally induced following the intravenous administrations of dextrose (unpublished observations). Specific reactions to intravenous dextrose or glucose are more apt to occur in cases of diagnosed corn sensitivity in which corn has been completely eliminated for a short time prior to intravenous therapy. There would appear to be less danger of such reactions when corn and corn products have been continued in the daily diet prior to the administra-

tion of corn sugar intravenously. From preliminary observations it may be said that clinical reactions from intravenous solutions of glucose or dextrose do not occur in all individuals in whom it is possible to precipitate a clinical response from oral feeding of corn sugar. This problem is under current investigation and will be reported subsequently.

Due to the frequency of corn sensitivity, as encountered in clinical allergy, the question should be reopened as to whether the almost universal practice of using corn sugar in infant feeding is a desirable procedure. Corn allergy is an important cause of infantile eczema and gastrointestinal allergic reactions in infants, and of other allergic responses in older children. In view of this and the relative ease with which clinical sensitivity to corn may be induced, it is our belief that corn sugar should at least be rotated with other sugars in infant feeding, as a prophylactic measure in keeping with the recently described observations of Rinkel.[15] If one sugar is to be used exclusively, cane sugar would appear to be preferable, as specific sensitivity to this product is less common. Carbohydrate derived from hydrolyzed tapioca or potato starch might also be used. Beet sugar must be considered as somewhat less desirable because of the relatively greater frequency of beet sensitivity as compared to cane sensitivity and the fact that the ingestion of beet sugar will cause symptoms in certain beet-sensitive patients.

A critical evaluation of the merits or demerits of the current vogue of employing corn syrup and malted corn products as sources of a carbohydrate in infant feeding, as far as it is related to the development of specific allergy, cannot be answered by us, as we see only allergic children. In the children that do come to our attention, corn sensitivity is a major if not the leading current food allergen.

There is no reason to believe that the problem of corn sensitivity is limited to certain geographic regions, in view of the widespread distribution of processed foods and the fact that the incidence of allergy to major foodstuffs is directly proportional to the incidence of specific foods in the diet. However, as adjudged from the eating habits prevalent in areas of the South and by the fact that a relatively higher percentage of native Southerners have been found corn sensitive as compared with a similar group living in the Northern Midwest, it seems probable that corn sensitivity might be more prevalent in that general area.

SUMMARY

Contrary to the generally prevalent impression, corn sensitivity is an exceedingly important clinical problem and ranks with wheat in the incidence of chronic food allergy. Under the proper experimental conditions, the ingestion of corn sugar by the highly corn-sensitive individual is apt to be followed by allergic symptoms.

Corn is, by all means, the most difficult food in the American diet to avoid. The treatment of corn allergy entails the elimination of all sources

of corn; in respect to corn sugar this means the exclusion of dextrose, glucose and commercial brands of corn sugar and syrup.

In view of the high incidence of corn sensitivity, the widespread practice of using corn syrup in infant feeding should be carefully investigated.

We agree with earlier work that corn sugar is not an effective anaphylactogen in guinea pigs.

REFERENCES

1. Coca, A. F.: Familial Nonreagenic Food-Allergy. Springfield, Illinois: Charles C. Thomas, 1943.

2. Hektoen, L., and Welker, W. H.: J. Infect. Dis., 53:309, 1933.

3. Randolph, T. G.: Fatigue of allergic origin to be differentiated from "nervous fatigue" or neurasthenia. Ann. Allergy, 3:418, 1946.

4. Randolph, T. G.: Allergy as a causative factor of fatigue, irritability and behavior problems of children. J. Pediat., 31:560, 1947.

5. Randolph, T. G.: Food allergy. M. Clin. North America, (Jan.) 1948.

6. Randolph, T. G.: Corn starch as an allergen; sources in food containers. (In press.)

7. Randolph, T. G.: The allergenicity of the so-called "inert ingredients" (excipients) of pharmaceutical preparations. (In press.)

8. Randolph, T. G., and Hettig, R. A.: The coincidence of allergic disease unexplained fatigue and lymphadenopathy; possible diagnostic confusion with infections mononucleosis. Am. J. M. Sc., 209:306, 1945.

9. Randolph, T. G., and Rawling, F. F. A.: Blood studies in allergy. V. Variations in total leucocytes following test feeding of foods; an appraisal of the individual food test. Ann. Allergy, 4:163, 1946.

10. Randolph, T. G., and Yeager, L. B.: The incidence of allergy to major foods. Proc. Central Soc. Clin. Research, 20:85, 1947.

11. Ratner, B., and Gruehl, H. L.: Anaphylactogenic properties of malted sugars and corn syrup. Am. J. Dis. Child., 49:307, 1935.

12. Rinkel, H. J.: Personal communications.

13. Rinkel, H. J.: Food Allergy. I. The role of food allergy in internal medicine. Ann. Allergy, 2:115, 1944.

14. Rinkel, H. J.: Food allergy. II. The technique and clinical application of the individual food test. Ann. Allergy, 2:504, 1944.

15. Rinkel, H. J.: Food allergy, IV. The function and clinical application of the rotary diversified diet. J. Pediat., 32:266, 1948.

16. Rinkel, H. J.: Migraine: review of the literature and diagnostic methods. Read before the Southwest Allergy Forum, New Orleans, 1944.

17. Rinkel, H. J.; Randolph, T. G., and Zeller, M.: Food Allergy. Springfield, Illinois: Charles C Thomas, (In press).

18. Rowe, A. H.: Food allergy. Its manifestations, diagnosis and treatment. J.A.M.A., 91:1623, 1928.

19. Rowe, A. H.: Allergic toxemia and migraine due to food allergy. California & West. Med., 33:785, 1930.

20. Rowe, A. H.: Food Allergy. Its Manifestations, Diagnosis and Treatment. With a General Discussion of Bronchial Asthma. Philadelphia: Lea and Febiger, 1931.

21. Urbach, E., and Willheim, R.: Infrequent, previously unreported nutritive allergy. Klin. Wchnschr., 11:1012, 1932.

THE USE OF BACITRACIN, A NEW ANTIBIOTIC, IN AEROSOL FORM

Preliminary Observations

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THE DISCOVERY of a new, readily available antibiotic always evokes interest in its potentialities and inevitably leads to a comparison with older existing antibiotics. Bacitracin, first reported by Johnson, Anker and Meleney[6] in 1945, has been no exception. This antibiotic, recovered from a strain ("Tracy I") of B. subtilis, is a neutral crystalline powder, water soluble and relatively heat stable (fifteen minutes at 100° C.). It is active *in vitro* chiefly against Gram-positive organisms, both aerobic and anaerobic, and ineffective against Gram-negative organisms, with the exception of the gonococcus and meningococcus. Some fungi and spirochetes[4] are highly susceptible. In these respects bacitracin resembles penicillin. It differs, however, in that bacitracin is poorly absorbed from topical applications, from the gastrointestional tract[2] and from the respiratory system, as will be shown later. This makes it, therefore, a drug of choice wherever local, concentrated antibiotic action is desired. This is especially true since bacitracin is locally nontoxic and nonirritating.[7] It has been recently demonstrated that powdered bacitracin may be applied to the surface of the brain without causing the convulsions which are characteristic of the application of penicillin, streptomycin and the sulfonamides. Moreover, it can be injected into the brain tissue or into the ventricles in a concentration of 1,000 units per c.c. without causing any evidence of irritation.[3]

There is the possibility, though, that bacitracin may have nephrotoxic effects following systemic administration.[8] However, this observation was made with certain lots of bacitracin and may be due to by-products of manufacture, which, it is hoped, will eventually be removed to produce a purer product.

Its use to date, therefore, has been practically confined to the local treatment of various types of surgical infections, pyodermas and ophthalmic infections.

Accordingly, the authors felt that bacitracin in aerosol form should be particularly beneficial in the treatment of sino-respiratory infection, which is primarily a local condition. The following additional advantages possessed by bacitracin tended to strengthen this belief:

1. It is relatively nonsensitizing as compared with penicillin.[8]
2. It can be used where penicillin hypersensitivity exists.

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3. It is not inhibited by tissues, secretions, or organisms which produce penicillinase and is, therefore, effective even in mixed infections.[7]

4. It apparently does not cause the production of any specific inhibitory enzyme, such as bacitracinase.

5. It appears to act synergistically with penicillin.[4]

6. It is not destroyed to any extent by propylene glycol, the vehicle employed in this study.[14]

This investigation was undertaken, therefore, to determine the value of bacitracin in aerosol form in the treatment of sino-respiratory infection.

MATERIAL AND METHODS

The bacitracin was dissolved in propylene glycol, which was the vehicle of choice primarily due to its ability to produce long-sustained aerosols. Furthermore, aqueous solutions were not practical due to the marked foaming induced by the detergent property of bacitracin. Besides, it was believed that propylene glycol had the following additional advantages: (1) unusual solvent properties that may possibly affect its penetration into mucous membranes as it does into skin; (2) the slight inhibitory action that it has in blood serum against some organisms.[9]

In order to accelerate solubility, the bacitracin was first dissolved in 2 to 3 c.c. of water and then the propylene glycol was added to make 20 c.c. This was always freshly prepared just prior to treatment. The dose of bacitracin varied from 12,000 units to 134,000 units, administered daily, most patients receiving 40,000 units. Patients were treated from four to twenty-four days. Where combined aerosols were employed, soluble crystalline penicillin G tablets in 100,000 unit dosage and in some cases, where indicated, streptomycin-calcium chloride complex, 0.5 gm. or 1.0 gm., were added. Treatment was continued whenever possible for one week after nasal secretions and/or sputum became nonpurulent in appearance. Results were recorded as "slight," "moderate," or "marked improvement"; "unimproved," or "worse." These were based on the degree of subjective improvement plus the improvement in physical signs, and the partial or complete clearing of nasal secretions and sputum.

Where nasal obstruction existed due to mucosal edema, a nasal decongestant was used preliminary to aerosol treatment. In patients with asthma, whenever necessary, an antispasmodic like aminophylline or Isuprel, singlely or in combination, by open inhalation was administered first in order to enhance the utilization of the antibiotic administered subsequently.[10]

The bacitracin was aerosolized by a combined steam generator and aerosolizer, and administered to the patient through a breathing box, thereby confining and conserving the aerosol, and in this way assuring the patient the maximum utilization of the antibiotic.[11] Besides, bacitracin given by the open method has a disagreeable odor and taste which are almost entirely eliminated in a closed system such as the breathing box. Infants and very small children were treated in a tent.[11]

TYPES OF CASES TREATED

As allergists, the authors recognized the existence of various extrinsic and psychogenic factors in many of the allergic patients, but only those with sino-respiratory infection were studied. This infection was either the sole cause of the patient's symptoms or complicated existing extrinsic allergic or psychogenic factors.

A total of 112 patients suffering with various types of sino-respiratory infections were treated. All of these were ambulatory patients from the private practices of the authors, except for four children treated on the pediatric ward of the Flower-Fifth Avenue Hospital. The conditions treated included acute and chronic paranasal sinusitis, acute and chronic bronchitis, bronchiectasis and infective asthma. These occurred either singly or in various combinations. The ages of patients ranged from twelve months to seventy-four years, and the duration of the condition treated varied from several days to about fifty years. Most of the patients had previously been treated elsewhere by the methods commonly used in allergic practice, and some had already been treated with penicillin aerosol.

All patients were given a complete physical examination, with emphasis on the sino-respiratory tract. Special attention was paid to the appearance of the nasal mucosa, the presence of nasal polyps, and the amount and character of the nasal secretions. In the bronchitic, bronchiectatic and asthmatic patient, the amount and character of the sputum were noted.

With few exceptions, x-rays were taken of the paranasal sinuses or chest, or both. Urinalysis was done every other day in selected cases, especially those receiving larger doses of bacitracin. This was deemed advisable in order to ascertain whether or not the bacitracin was exerting any nephrotoxic action. In a group of selected cases, bacteriologic studies including bacterial sensitivity to the antibiotics were made with organisms cultured from the throat and, in some cases, from the sputum or nose. Absorption studies for bacitracin were limited to eight cases and will be presented later.

RESULTS

To simplify analysis, the conditions treated were divided into "paranasal sinus infection," "respiratory infection," including bronchitis, bronchiectasis and infective asthma, and "sino-respiratory infection," a combination of the two.

A total of 112 patients were treated. Of these, only 100 are reported here due to insufficient data on the remaining twelve cases. Of these 100 cases, seventeen were treated with bacitracin alone, the remaining eighty-three receiving the combined bacitracin-penicillin aerosol. The results following treatment are tabulated in Tables I and II.

Although no accurate evaluation can be obtained from such a small series treated with bacitracin only, it is, nevertheless, interesting to ob-

TABLE I. RESULTS OBTAINED BY TREATMENT WITH BACITRACIN AEROSOL OF 17 PATIENTS WITH SINO-RESPIRATORY INFECTION

Type of Infection	No. of Patients	Marked Improvement		Moderate Improvement		Slight Improvement		Unimproved		Worse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Paranasal Sinusitis	8	3	37.5	3	37.5	1	12.5	1	12 5	0	0
Respiratory	1	1	100.0	—	—	—	—	—	—	0	0
Sino-respiratory	8	3	37.5	3	37.5	—	—	2	25.0	0	0
Totals	17	7	41.2	6	35.3	1	5.9	3	17.6	0	0

TABLE II. RESULTS OBTAINED BY TREATMENT WITH COMBINED BACITRACIN AND PENICILLIN AEROSOL, OF 83 PATIENTS WITH SINO-RESPIRATORY INFECTION

Type of Infection	No. of Patients	Marked Improvement		Moderate Improvement		Slight Improvement		Unimproved		Worse	
		No.	%	No.	%	No.	%	No.	%	No.	%
Paranasal Sinusitis	37	21	56.8	7	18.9	4	10.8	5	13.5	0	0
Respiratory	12	8	66.7	3	2.50	—	—	1	8.3	0	0
Sino-respiratory	34	26	76.5	6	17.6	—	—	2	5.9	0	0
Totals	83	55	66.3	16	19.3	4	4.8	8	9.6	'0	0

serve in these tables the favorable results (moderate and marked improvement) obtained with bacitracin alone and with combined bacitracin-penicillin—76.5 per cent and 85.6 per cent, respectively, as compared to 73 per cent obtained with penicillin only, on a comparative dosage basis as previously reported.[12]

Table III presents summaries of a selected group of patients treated with bacitracin singly or in combination. These were chosen to illustrate the type of case treated and the indications for the use of bacitracin. These included previously treated patients who were considered as failures with penicillin aerosol, and instances of sensitivity to penicillin. Patients were improved for a period lasting from two weeks to about one year. This factor depended, in many instances, upon the frequency of common colds, which either served to flare up a mild, subclinical focus or produce a new infection.

BACTERIOLOGIC STUDIES

In order to evaluate the result of specific antibiotic therapy, it is desirable to know the identity of the organisms and their responsiveness to the antibiotic by *in vitro* testing (sensitivity tests). This was undertaken in a number of patients prior to treatment or whenever information was desired, during or after termination of treatment, in order to evaluate the therapeutic agent administered.*

Originally, cultures were taken from the nose and throat and, in some

*Dr. Norman Molomut of the Biologic Laboratories, Brooklyn, N. Y., performed the bacteriological and sensitivity studies.

TABLE III. RESUME OF SELECTED CASES TREATED WITH BACITRACIN AEROSOL—SINGLY OR IN COMBINATION

No.	Patient	Sex	Age	Symptoms and Diagnosis	Duration of Complaint	Culture	Sensitivity Tests	Treatment	Total Dose (x 1000)	Clinical Results	Comment
1	E.F.	F.	59	Asthma Sinusitis Bronchiectasis Diabetes Nasal polyp	1 year	γ Strep.	Pen. 15 u. mod. sens. St. 500 u. resistant	Pen. 100 M/d. 3 weeks Pen. 100 M/2d. Strep. 1 gm. 500 M. to 300 M./d	2100 600 } 6 gm. }	Mod. imp. No further imp.	Prolonged treatment with penicillin gave moderate improvement. Streptomycin ineffective. Bacitracin finally resulted in clearing of infections. No skin testing. No immunotherapy.
2	R.L.	M.	7	Chr. sinusitis Allergic rhin. Nas. stuffiness Discharge and chronic cough	2 yrs.	Staph. γ Strep. Gm.† Bacilli	Pen. 15 u. resistant St. 500 u. mod. sens.	Bac. 6000 b.i.d.	5000	No further imp.	
3	M.G.	M.	5	Asthmatic bronchitis Sinusitis Laryngitis Chronic cough	5 months 3 years			Bac. 40 M/d.	252	Marked imp.	
4	H.G.	M.	18	Ac. sinusitis Nas. stuffiness and P.N.D.	1 week Since infancy			Pen. 100 M/d. 3 weeks Pen. 100 M/d. Bac. 20 M/d. 2 weeks	896 3000 3000 300	Marked imp. Mod. imp. Marked imp.	X-ray: Clouding of left ethmoid and antrum. Previously taken 100 M. penicillin orally for 24 days with no relief. Improvement noted by 2nd week. Remained well for 6 months. No skin testing. No immunotherapy.
5	F.J.	F.	43	Sinusitis Bronchitis Bronchiectasis Asthma Nasal polyp	11 years 3 years	Staph. Strep.	Pen. 15 u. Str. 500 u. resistant	Pen. 200 M/d. Bac. 41 M/d. 11 days	2200 451	Marked imp.	Moderate improvement with penicillin by end of 1st week. Complete relief when bacitracin was added. Synergism? Or additional penicillin? No skin testing. No immunotherapy. Well for 1 year.
6	E.B.	F.	52	Sinusitis Asthma Psychoneurosis Pneumonitis	3 years 1 week			Amin.-Isup. aerosol Pen. 100 M/b.i.d. Bac. 45 M/b.i.d. Pen. 200 M/d. Bac. 40 M/d.	2700 810 3500 480	Marked imp. Marked imp.	Acute symptoms subsided by 3rd day. Stuffiness and postnasal drip, cleared for first time in years. X-rays taken showed frontal sinusitis, cleared on re-examination after treatment. Previous treatment with penicillin aerosol in Arizona without relief. Marked improvement with combined therapy. Not completely relieved; organisms resistant to penicillin and streptomycin. Previously treated with penicillin aerosol, with excellent results. Pneumonitis with X-ray clearing following combined therapy.

7	A.W.	F.	9	Sinusitis (?) Chr. tonsilitis Chronic cough	2 years			Pen. 100 M/d. Bac. 40 M/d.	1100 440	Marked imp.	Tonsils markedly enlarged, obstructive and congested. Scheduled for T. & A. Complete relief of symptoms and marked reduction in size of tonsils.
8	S.S.	F.	19	Mixed asthma (Ragweed pollenosis sinusitis)	2 years			Amin. and Isup. Aerosol Pen. 100 M/d. Bac. 42 M/d.	 2500 250	Marked imp.	Patient had been taking penicillin aerosol at home—50 M. b.i.d. for 6 weeks (7 million units) without relief. Successful prophylaxis later for a cold. Relieved by combined penicillin and bacitracin. Also given ragweed injections.
9	R.N.	M.	7	Asthma Sinusitis	1 year 5 years			Pen. 100 M } b.i.d. Bac. 40 M }	2300 440	Marked imp.	Status asthmaticus. Previously treated in Baltimore with applications of radon to nasopharynx with temporary relief. Now free of asthma for 6 months. No skin testing. No immunotherapy.
10	G.E.	M.	51	Asthma Sinusitis Bronchitis }	1 month 5 years			Amin. and Isup. Aerosol Pen. 100 M } d. Bac. 12 M } Bac. 12 M	 300 36 60	 Moderate imp. Marked imp.	Excellent response to combined aerosol therapy. Developed a rash on face due to penicillin while under treatment. Discarded penicillin, and continued with bacitracin until all infection disappeared. No testing. No immunotherapy. Well for almost 1 year.
11	A.S.	M.	50	Asthma Sinusitis Chronic bronchitis }	5 years 10 years			Amin. and Isup. aerosol Pen. 100 M } d. Bac. 40 M } Same w/Strep. 2 days Pen. 300 M/d. and 200 M/d.	 3800 980 2 gm. 2800	Marked but temporary relief Worse Marked imp.	At first good results with penicillin and bacitracin, but had relapse, and when streptomycin was added he was definitely worse. Penicillin in large doses resulted in immediate and marked improvement, which continues. No testing. No immunotherapy.
12	B.O.	M.	42	Chronic sinusitis	15 years	Strep. Staph. Coliform bacilli	All organ. sens. to Pen. Bac. and Strep.	Bac. 67/d	737	Marked imp.	Patient had been previously treated at home with his child in bathroom, in an attempt to eradicate his sinus infection, as well as that of the 5-year old patient. Both did well. Father developed a rash on face. Patch-testing with penicillin was positive. Propylene glycol was negative. Prompt response to bacitracin. Penicillin had previously given 6 months relief.

instances, from the sputum, but this was discontinued since the throat cultures seemed to provide the best information. In several instances, the cultures were grown in media containing the patient's blood, in addition to the routine rabbit's blood media, since it reflected the patient's immunologic response. It was noted in some instances that a hemolytic organism on rabbit blood medium showed no hemolysis with the patient's blood, indicating some degree of immunity; and, conversely, no hemolysis was noted with rabbit blood but was observed on the patient's own blood and, therefore, revealed a lack of immunity and a greater need for antibiotic therapy.

TABLE IV. CLASSIFICATION AND FREQUENCY OF ORGANISMS CULTURED FROM THE THROATS OF 38 PATIENTS PRIOR TO TREATMENT

Organism	Number of times cultured
Streptococci:	
Alpha Hemolytic	5
Beta Hemolytic	13
Gamma (Non-hemolytic)	18
Staphylococci:	
Non-hemolytic	17
Hemolytic (Beta type)	4
N. Catarrhalis	20
Proteus Vulgaris	4
Coliform Bacilli	3
Diphtheroids	3
Pneumococci	1
Tetragenous	1
Hemophilus	1

Table IV lists the organisms identified in thirty-eight patients prior to treatment. Interest centered particularly on the streptococci and staphylococci, in view of their susceptibility to penicillin and bacitracin. The unusual presence of Gram-negative organisms, such as proteus vulgaris and coliform bacilli, was attributed to earlier treatment with penicillin aerosol.

Following the identity of the organisms obtained on culture, they were tested as a combined flora with penicillin, bacitracin, streptomycin and sulfacetimide respectively, to determine their sensitivities. The final concentrations employed in each culture were: penicillin, 1 u./c.c.; bacitracin and streptomycin, 10 u./c.c.; and sulfacetimide, 0.6 mg./c.c.

Inhibitory action was observed at six to eight hour and twenty to twenty-four hour intervals, since it had been noted on occasion that, whereas an inhibiting effect was exhibited for the first six to eight hours, there was a tendency to overcome the antibiotic and have no inhibition in twenty to twenty-four hours. In some cases, this temporary inhibition was noted with only one antibiotic agent, and therefore another one was employed which was more effective. In two instances it was necessary to treat every six hours, day and night, in order to effect complete inhibition. In most instances, however, this was unnecessary, since the inhibition seen during the first eight hours continued through twenty-four hours and enabled us to treat the patient once daily.

Table V records the total number of organisms (ninety) obtained by pharyngeal culture of thirty-one patients prior to treatment, along with the individual sensitivities of each of these organisms to penicillin, baci-

TABLE V. INHIBITORY* ACTION OF PENICILLIN, BACITRACIN AND STREPTOMYCIN AGAINST 90 ORGANISMS OBTAINED BY PHARYNGEAL PRE-TREATMENT CULTURES OF 31 PATIENTS

Number of Organisms:	Number	Per Cent
Obtained by Culture	90	100
Inhibited by Penicillin	64	70.1
Inhibited by Bacitracin	63	70.0
Inhibited by Streptomycin	80	88.8
Inhibited by Penicillin and not others	0	0.0
Inhibited by Bacitracin and not others	1	1.1
Inhibited by Steptomycin and not others	4	4.4
Inhibited by Bacitracin and not Penicillin	9	10.0
Inhibited by Penicillin and not Bacitracin	10	11.1
Equally inhibited by Penicillin and Bacitracin	52	57.6

*Concentration of antibiotics/c.c. in final broth dilution for inhibition studies were:
Penicillin, 1 unit
Bacitracin, 10 units
Streptomycin, 10 units

tracin and streptomycin. The latter showed surprising antibiotic activity (88.8 per cent) in this series, as compared with penicillin (70.1 per cent) and bacitracin (70 per cent). This is probably accounted for by the fact that more than half of these patients (seventeen out of thirty-one) had been subjected to penicillin aerosol therapy previously. This is inferred from the observation of patients who, treated for the first time with penicillin or bacitracin aerosol, ultimately exhibit Gram-negative organisms (coliform bacilli, proteus vulgaris, et cetera) following termination of treatment.

No organisms were observed which were inhibited by penicillin only; one was inihibited only by bacitracin, and nine organisms not inhibited by penicillin were sensitive to bacitracin. Conversely, ten organisms were not inhibited by bacitracin but were definitely sensitive to penicillin. More than half (fifty-two) of the organisms were equally sensitive to penicillin and bacitracin.

Parenthetically, it may be indicated that there were other instances of bacitracin sensitivity not recorded in Table V. Thus in Cases 1, 2 and 5 of Table III there are recorded successful therapeutic results with bacitracin after failure with penicillin and/or streptomycin, and in which cultures and sensitivity tests had indicated poor or no inhibition with penicillin or streptomycin. No bacitracin inhibition tests were performed, and these cases were not included in Table V. Presumably the organisms cultured were inhibited exclusively by bacitracin according to clinical response.

The inhibitory action of the antibiotics as reported in these studies does not, however, take into account the fact that both the bactracin and streptomycin were employed in concentration of 10 u./c.c., in sharp contrast to 1 u./c.c. of penicillin. Different concentrations may have led to different results.

CORRELATION OF CLINICAL RESULTS WITH BACTERIOLOGIC CHANGES

Is there a correlation of clinical results obtained with bacteriologic changes noted following treatment? An attempt was made to answer this question by the observation of seventeen patients (Table VI) in whom

TABLE VI. CORRELATION OF CLINICAL RESULTS AND BACTERIOLOGICAL CHANGES IN 17 PATIENTS TREATED WITH BACITRACIN—SINGLY OR IN COMBINATION

Case	Name	Diagnosis	Pre-Trmt. Culture	Sensitivity Studies†				Treatment	Post-Trmt. Culture	Bacteriologic Changes	Clinical Results
				Pen.	Bac.	Str.	Sul.				
1	Fo.	Asthma Sinusitis	γ strep. Staph P.Vulgaris	+ + −	+ + −	− + +	+ + ±	Pen. Bac. & Strept.	γ strep. Gm-dip. P.Vulgaris	Elim. of staph.	Marked imp.
2	Ti.	Nasal polyp Sinusitis	γ strep. Gm-dip. Staph Gm-bac. (vibrion)	+ + + +	+ + + +	+ + + +	− + + +	Pen. & Bac.	Gm-dip. γ strep. staph.	Vibrion lost	Temp. imp.
3	Mc.	Sinusitis	*B strep. *Hemo. staph Gm-dip.	− + −	+ + −	+ + +	− + +	Pen. & Bac.	γ strep. staph. Gm-dip.	Elim. of Hem. staph & strep.	Marked imp.
4	No.	Sinusitis Allergic-rhinitis	γ strep. Staph (hemo.) Gm-dip.	+ + +	+ + +	+ + +	+ + +	Pen. & Bac.	γ strep. Gm-dip.	Staph. elim.	Marked imp.
5	Sh.	Chronic sinusitis	α strep. B. strep. Gm-dip.	± ± ±	± ± ±	± ± ±	− − −	Pen. & Bac.	Gm-dip. γ strep.	α strep. & B. strep. elim. γ strep. appeared	Marked imp.
6	Sk.	Sinusitis Bronchi-ectasis Asthma	B. strep. Staph.	− −	± +	− ±	− −	Bac.	γ strep. staph. B. strep.	None	Worse
7	Myr. S.	Chronic sinusitis	**Hemo. staph γ strep.	+ ±	+ +	+ ±	− −	Bac.	Hemo. staph γ strep. Gm-dip.	No sig. changes	Marked imp.
8	Mek. S.	Acute sinusitis	**Hemo. staph γ strep. Gm-dip.	+ + +	+ + +	+ − +	+ − +	Pen. & Bac.	Hemo. staph γ strep. Gm-dip.	None	Marked imp.
9	Sch.	Acute sinusitis Allergic rhinitis	B. strep. Staph Gm-dip.	+ + +	− + +	+ + +	− − +	P&B & Str.	Gm-dip. γ strep.	B. strep. & staph. elim.	Marked imp.—short duration
10	Sch.	Nas. polyp Sinusitis Allergic rhinitis(?)	γ strep. Gm-dip. Pneumo-cocci. Colif. bac.	+ − − −	+ + + −	+ + + +	+ + − +	Bac.	γ strep. Staph. Gm-dip. Colif. bac.	Pneumo-cocci elim. Staph. appeared	Moderate imp.
11	Sc.	Sinusitis	Gm-dip. Gm+dip. (Hemo) Staph	+ − −	+ + +	+ + +	+ − +	Bac.	γ strep. Gm-dip. Diphther-oids	Elim. of gm+dip. & staph. Appearance of γ strep. & diphther-oids	Marked imp.
12	Wi.	Asthma Sinusitis Bronchi-ectasis Nasal polyps	Gm+dip. Staph Colif. bac. strep.	Not	perf	orm	ed	Bac.	Staph Gm+dip. Colif. bac.	Reduction in no. of Colif. bacilli	Marked imp. short duration
13	Un.	Asthma Sinusitis Bronchi-ectasis Nasal polyp	Gm-dip. Staph Colif. bac.	Not	perf	orm	ed	Bac.	Staph Colif. bac.	Reduction in no. of Colif. bacilli	Moderate imp.
14	Si.	Sinusitis Asthma	B. strep. Staph Diphth. Gm-dip.	+ + + +	+ + + +	+ + + +	+ + + +	Pen.	Strep. Staph Gm-dip. Occ. pneum.	Elimin. of hemol. strep. & diphther-oids. Appearance of strep. & pneumococci	Marked imp.

TABLE VI. (*Continued*)

15	Ol.	Chronic sinusitis Allergic rhinitis?	γ strep. Staph Colif. bac.	+ + +	+ − +	+ + +	+ − +	Bac.	B. strep. Staph Proteus Colif. bacilli	Bacteriologically worse. Appear. of hemol. strep. & P. vulgaris	Marked imp.
16	Wit.	Chronic sinusitis Allergic rhinitis	γ strep. Gm-dip. Gm-bacilli (Hemophilus) Diphtheroids	+ + + +	+ + + −	+ + + +	+ − − +	Pen. & Bac.	B. strep. Gm-dip. Diphther. Gm-bacilli (Hemophilus) P. vulgaris	Bacteriologically worse. Appear. of hemol. strep. & P. vulgaris	Marked imp.
17	Zin.	Sinusitis Asthma	γ strep. Gm-dip.	+ +	+ +	+ +	+ +	P&B & S.	Gm-dip. Colif. bacilli	Disappearance of γ strep. Appearance of Colif. bacilli	Un-improved

†Code to Sensitivity Studies: +inhibitory action; −no inhibitory action; ± partial or temporary inhibition.
*Hemolysis on patient's blood and not on rabbit's blood.
**Hemolytic staph. found in two sisters and subsequently isolated from the mother.

adequate culture studies were obtained before and after treatment. One of these patients was treated with large doses of penicillin only (after preliminary treatment with penicillin and bacitracin), seven with bacitracin only, six with a combination of penicillin and bacitracin, and three with these antibiotics plus streptomycin. Based on this small series of patients, it was noted that there was some limited correlation between the bacteriologic and clinical improvement. Thus, of fifteen patients who showed definite improvement, nine showed corresponding change in the organism found and suspected of pathogenicity. In two other instances, there was no change in the original organisms, but there was a definite reduction in number as judged by the number of colonies per culture plate. There may, therefore, be a quantitative change which may be of importance. Likewise, it was noted that among those clinically improved[15] there were two instances where, on a bacteriologic basis, they were considered possibly worse. One patient who was clinically unimproved showed no bacteriologic change.

The series of patients in whom pre-treatment and post-treatment cultures were obtained is too small at the present writing to draw any definite conclusions concerning the correlation between clinical results and bacteriologic changes.

ABSORPTION OF BACITRACIN VIA THE LUNGS

Studies of blood absorption of penicillin[11] and streptomycin aerosols[13] have previously been made by the senior author in collaboration with others, which have indicated that these antibiotics are readily absorbed from the respiratory tract. It was, therefore, of interest to investigate the absorption of bacitracin aerosol.

Seven normal males with good vital capacities were, therefore, treated with bacitracin (67,000 units), utilizing the breathing box method, and a

single blood sample was taken thirty minutes from the onset of treatment, which lasted about fifteen minutes. In the aforementioned studies with penicillin and streptomycin, maximum blood levels were obtained by that time. In none of these cases was any bacitracin demonstrable in the blood.† One asthmatic patient (Case 6, Table VI) who had been getting large doses of bacitracin was also examined for the presence of bacitracin in his blood one hour after treatment with 67,000 units, and likewise failed to show any absorption. This would indicate that the clinical evaluation of bacitracin as an aerosol would be an expression of its topical action, in sharp contrast to penicillin and streptomycin aerosols, which have twofold action, topical and systemic, following absorption.

There is the possibility that bacitracin may be absorbed to some degree in patients suffering from bronchiectasis.* This may possibly be accounted for by increased absorption across inflamed or altered mucous membranes. Care should therefore be exerted in the treatment of these patients by frequent urinary examinations in order to avoid possible nephrotoxic action.

ADVERSE REACTIONS

Although there was no definite proof of unfavorable reactions to bacitracin, it was suspected in two cases. One patient treated with bacitracin aerosol, who was also given bacitracin lozenges because of a pharyngitis, complained of a burning sensation in the throat following its use. She subsequently developed a similar sensation retrosternally when bacitracin aerosol was administered. This patient originally had complaints suggestive of a tracheitis along with asthma and sinusitis, and it is therefore difficult to evaluate the reaction to bacitracin aerosol. There was a definite unfavorable reaction to the lozenge, and, therefore, bacitracin in any form was discontinued.

Another patient on combined bacitracin-penicillin aerosol reported nasal irritation after the third treatment, which might have been caused by either antibiotic. Although the sinusitis was clinically improved, treatment was discontinued after the fifth day because the patient had to leave town, which prevented the discovery of the cause of the discomfort.

As for penicillin reactions, it is noteworthy that of the eighty-three patients only one developed a black tongue while under treatment with large doses of penicillin every six hours around the clock, including penicillin powder twice daily at home (Case 5, Table VI). Another patient developed a circumoral contact dermatitis on combined bacitracin-penicillin which disappeared completely with the removal of penicillin. Treatment was continued with bacitracin, and a cure was ultimately effected (Case 10, Table III).

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and Surgeons, for these assays.
*Personal communication from Dr. Frank L. Meleney.

DISCUSSION

From our small series of patients treated exclusively with bacitracin, no definite conclusions can be drawn. It does suggest, however, the possibility that bacitracin aerosol may be equally as effective as penicillin aerosol. This conclusion must of necessity be qualified, due to the fact that the optimum dosage of bacitracin has, as yet, not been determined, and therefore it is possible that some of our patients may have been undertreated, making a true comparison impossible at this time. One can be more definite, however, regarding the combined action of bacitracin and penicillin aerosol, as compared with penicillin aerosol alone, in view of the larger series of eighty-three patients observed. Here we have noted a definite improvement in results. On this combined therapy, the favorable (moderately and markedly improved) cases reached 85.6 per cent compared to 73 per cent in a comparable series on penicillin alone. (This series included some of the earlier cases treated with penicillin, some of whom were limited to 500,000 units, which would be considered inadequate today.) This strongly suggests a clinical synergistic action and tends to confirm the bacteriologic synergism previously reported.[1,15] It is also possible that an additional explanation of improved results is due to the particular value of bacitracin in mixed infections, where the enzyme penicillinase is more likely to be produced, inhibiting the action of penicillin but not of bacitracin.[7]

The authors are cognizant of the limitations of the bacteriologic methods employed in this investigation. *In vitro* studies eliminate the host factor which is of great importance. Also, emphasis was placed on a pharyngeal culture, whereas cultures of the nose, throat and sputum may have been more informative. Then, again, a single method of culture was employed, and it is conceivable that some organisms may have found the medium employed unfavorable for growth and thus escaped detection. The question also arises whether the organisms obtained by culture of material from the surface of a membrane are actually the noxious agents since, in chronic disease, the organisms may be deep-seated within the mucous membrane. And, finally, what is a normal flora and when is a specific organism pathogenic? Some organisms, such as N. catarrhalis or nonhemolytic streptococci, may be considered as nonpathogens for most people, but is that true for all? We have observed hemolytic staphylococci in two sisters (Table VI, Cases 7 and 8) who were clinically ill and who improved remarkably with antibiotic therapy, yet the post-treatment cultures still showed hemolytic staphylococci. Are these organisms no longer pathogenic or is this only a transient state? Many questions still remain to be answered.

It has been the impression of the authors that frequent infections of the respiratory tract, particularly in children, were due to contact with carriers in the immediate family.[11,12] This was dramatically shown in the

cases cited above, in which hemolytic staphylococci were cultured from two sisters—one acutely and the other chronically ill with respiratory infections. It was inferred that the infection had spread from the older sister (chronic infection and some immunity) to the younger sister who was acutely ill and apparently with little or no immunity. But where did the older sister get the infection? Pharyngeal cultures were made, therefore, of both the mother and father, and the former was indicted as a possible carrier by the presence of a hemolytic staphylococcus, presumably the same found in the children.

This observation is of importance since it confirms bacteriologically a clinical impression previously voiced, and adds emphasis to the importance of treating simultaneously other members of the family, when necessary, in order to reduce the illness of a susceptible (nonimmune) patient. The bathroom method for aerosol therapy, previously described, is the answer for the younger child and a suspected parental or sibling carrier.

From a prophylactic angle, in reference to the cases cited above, it may be important to treat the mother at the first sign of a "cold," in order to prevent possible reinfection in the children. Likewise, the children, now well, will be given prophylactic aerosol therapy at the first sign of a "cold" in order to obviate a return of the original complaint.[11,12]

Bacitracin is of particular value not only because of its local topical action which enhances its value as an aerosol but also because it may be used in patients sensitive to penicillin. Thus, Case 12 in Table III exemplifies successful therapy with bacitracin in an individual who was previously found hypersensitive to penicillin. Likewise, Case 10 in the same table revealed a hypersensitivity to penicillin while under treatment with combined bacitracin-penicillin aerosol. Penicillin was discontinued, and the bacitracin alone achieved the desired therapeutic results.

In previous reports, one of us (S.J.P.) emphasized the importance of improving the vital capacity of patients with infective asthma, prior to aerosol treatment with antibiotics.[11] We wish to re-emphasize this point and advise the use of aminophylline and/or Isuprel, either in single or combined aerosols, to insure better utilization of the subsequent antibiotic.

The poor absorption of bacitracin from the respiratory system should minimize the fear of nephrotoxicity or any other systemic reactions. In our series of cases, urinalysis revealed an occasional slight, transient albuminuria. One patient treated under our supervision, but not included in this study because of inadequate therapy, manifested some evidence of the nephrotoxic action of bacitracin. She was given aerosol therapy with bacitracin (40,000 units twice daily) for only two days, and, in addition, bacitracin was administered intramuscularly, 10,000 units twice daily. She promptly developed albuminuria and many casts in the urine. Treatment was discontinued, and within a week the urine cleared.

One is led to speculate as to just what happens to substances such as

bacitracin, which are not readily absorbed from the lower respiratory tract. Studies with uranium oxide, administered to animals as an aerosol, show that when the aerosol particles are 0.5 micron or less in size, the aerosol is diffusely distributed throughout the bronchial tract and alveoli. Within twenty-four hours the bronchial system is cleared of the insoluble uranium oxide by ciliary action, and is eliminated through the gastrointestinal tract.[5] The aerosol may remain deposited in the alveoli, however, for months. This may not be true of bacitracin, inasmuch as bacitracin is a short-chain polypeptide,[1] which would probably be digested in time by enzymatic action.

CONCLUSIONS

1. Preliminary observations with bacitracin indicate that it may be safely and effectively employed in aerosol form for the treatment of sinorespiratory disease.

2. Although a true evaluation of bacitracin aerosol cannot be made at this time, in combination with penicillin it has been very effective and suggests synergistic action of these antibiotics.

3. Bacitracin is especially indicated: (a) when the cultured organism is sensitive to bacitracin but not to penicillin, as was shown in nine of ninety instances in our series; (b) in penicillin hypersensitivity or intolerence; (c) in mixed infections in which the neutralizing action of penicillinase may be a factor.

4. No absorption of bacitracin from the respiratory system could be demonstrated in these studies.

5. The definite value of bacterial studies, including bacterial sensitivity, is indicated.

6. No absolute correlation could be found between changes in bacterial flora and clinical results.

7. In repeated reinfections, especially in children, it may be important to search for and to treat any suspected carriers.

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REFERENCES

1. Barry, G. T.; Gregory, J. D., and Craig, L. C.: The nature of bacitracin. J. Biol. Chem., 175:485, (Aug.) 1948.
2. Bond, G. C.; Vanderbrook, M. J.; Wiley, J. L., and Nook, M. A.: Oral administration of bacitracin. Proc. Soc. Exper. Biol. & Med., 68:395, (June) 1948.
3. Cone, William: Quoted by F. L. Meleney in: Copy of the Final Report sent to Office of the Surgeon General, January 1, 1949.
4. Eagle, H., and Fleischman, R.: Therapeutic activity of bacitracin in rabbit syphilis and its synergistic action with penicillin. Proc. Soc. Exper. Biol. & Med., 68:415, (June) 1948.
5. Hamilton, J. G.: The metabolism of the fission products and the heaviest elements. Radiology, 49:325, 1947.
6. Johnson, B. A.; Anker, H., and Meleney, F. L.: Bacitracin: a new antibiotic produced by a member of the B. subtilis group. Science, 102:376, (Oct. 12) 1945.

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DIATRIN HYDROCHLORIDE

A New Antihistaminic Agent for the Treatment of Pruritus and Allergic Dermatoses

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DIATRIN hydrochloride (N,N-dimethyl-N'-phenyl-n'-(2-thi-enylmethyl)-ethylenediamine monohydrochloride), a histamic antagonist of proven value in experimental animals,[2] had such a low incidence of side effects in recent clinical investigations[1] that a therapeutic trial was undertaken. A variety of pruritic and allergic dermatoses were chosen. The Diatrin was administered in 50 mg. tablets, both plain and sugar coated.*

RESULTS OF TESTS

Urticaria.—There were fourteen patients with urticaria, in five of whom it had followed the administration of penicillin. Of the latter, four were relieved in varying degrees—one completely, one moderately, and two slightly. One was not helped at all. The dose for all five patients was the same, 150 mg. daily. In the nine with urticaria from other causes, two of whom had angioneurotic edema as well, the dose administered to four was 200 mg., and to five, 400 mg. daily. Relief in all of these patients was prompt and complete.

Neurodermatitis.—Of three patients with disseminate neurodermatitis, one obtained marked relief on 400 and 1,000 mg. daily, one had moderate relief on 200 mg. per day, and one patient found 50 mg. at bedtime sufficient for his needs.

Dermatitis Medicamentosa.—Of three patients with generalized dermatitis medicamentosa, one did not respond, one exhibited moderate relief of pruritus, and one had varying degrees of relief on different occasions. This last patient had purpura following penicillin therapy.

Atopic Eczema.—Ten patients with atopic eczema were treated with 200 to 800 mg. of Diatrin a day for from eight to forty-seven days. Four were helped in varying degrees, and six failed to show any response. Of the former, two had only slight relief, one moderate relief from pruritus, and one had sporadic relief, sometimes complete and sometimes slight. The degree of relief was not dependent upon the dosage: for example, one patient was receiving 800 mg. daily with no effect, while one who received 250 mg. had very satisfactory results.

Erythema Multiforme.—Of three patients with erythema multiforme two showed no response to 200 mg. each day, but one had marked relief on the same dosage, with disappearance of the eruption in four days.

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*Diatrin hydrochloride was supplied by William R. Warner and Co., Inc. of New York, N. Y.

TABLE I

Diagnosis	Number of Patients	Relief			No Relief	Results	Side Effects
		Complete	Moderate	Slight			
Urticaria	9	9	—	—	—	100%	None
Penicillin Urticaria	5	1	1	2	1	80%	None
Neurodermatitis	3	2*	1	—	—	100%	None
Dermatitis Medicamentosa	3	1*	1	—	1	66%	None
Atopic Eczema	10	1*	1	2	6	40%	None
Erythema Multiforme	3	1	—	—	2	33.3%	None
Dermatitis Venenata	30	3	4	2	21	30%	2 patients with nausea, 2 with fever, 1 with vomiting, 1 with diarrhea, 1 with generalized burning of skin.
Infectious Eczematoid Dermatitis	4	—	—	1	3	25%	1 patient had nausea and urinary frequency.
Recurrent Vesicular Eruptions	9	1	—	—	8	11%	1 patient had nausea and vomiting.
Miscellaneous	4	2	1	—	1		
Total	80	21	9	7	43		

*The percentage values are somewhat misleading—first, because they are based on a small number of patients, and second, because the degree of relief varied and was in some cases inconstant.

Dermatitis Venenata.—Thirty patients with contact dermatitis were included in this series. Nine of these were helped; twenty-one were not. The dosage varied from 100 to 600 mg. daily. Here again there seemed to be no direct relationship between the daily dosage and results. For example, although one patient on 100 mg. per day was much more comfortable, there was no effect at all on other patients receiving the same dosage. One patient who was getting 600 mg. per day was completely relieved of pruritus; another on the same dosage felt no diminution in the intensity of pruritus.

Infectious Eczematoid Dermatitis.—There were four patients with intensely pruritic infectious eczematoid dermatitis. In three the itching was not allayed at all by 400 to 1,000 mg. daily, although one on 400 mg. felt somewhat better.

Recurrent Vesicular Eruptions.—This series included nine patients with recurrent vesicular eruptions of the hands and feet, not of the contact type. In eight of these there was no effect whatever from 100 to 400 mg. daily. The remaining patient had marked relief on 100 mg. per day.

Miscellaneous.—Diatrin hydrochloride was also given in doses of 100 mg. per day to two patients with herpes simplex, both of whom benefited. One patient with extensive insect bites received 200 mg. daily with no benefit. One patient with a pruritic pityriasis rosea took 100 mg. at bedtime and found the intensity of the pruritus relieved sufficiently to permit sleep.

SIDE EFFECTS

Minor side effects developed in seven patients; these included nausea, vomiting, diarrhea, urinary frequency, and generalized burning of the skin. In only three patients was it necessary to discontinue the drug. All side effects stopped promptly on cessation of the drug. As in previous experience with Diatrin,[1] the plain tablet was responsibile for all untoward reactions, the sugar-coated tablet in this admittedly small series being responsible for none. Aside from masking the bitter taste of the drug and thereby decreasing the incidence of nausea and vomiting, it is difficult to understand why a thin sugar coating should prevent the occurrence of these side effects. Possibly in a larger series, they would be more evident. However, even including those untoward effects for which the plain tablet was responsible, the percentage of side actions was remarkably low.

SUMMARY AND CONCLUSIONS

Diatrin hydrochloride was administered to eighty patients with allergic and pruritic dermatoses. Best results were obtained in urticaria, although other dermatoses responded to a lesser degree. These results are similar to those obtained with other antihistaminic agents. The incidence of side effects, however, was much lower than with other histamine antagonists at present in general use.

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REFERENCES

1. Combes, F. C.; Zuckerman, R., and Canizares, O.: Diatrin hydrochloride, clinical and toxicologic studies of a new antihistaminic agent. (In press.)
2. Ercoli, N.; Schachter, R. J.; Hueper, W. C., and Lewis, M. N.: The toxicologic and antihistaminic properties of N,N'-dimethyl-N'-phenyl-N'-(2 thienylmethyl) ethylenediamine hydrochloride (Diatrin). J. Pharmacol. & Exper. Therap., 93:210, (June) 1948.

POSSIBLE USES OF A DELAYED-ACTION ANTIHISTAMINIC

Clinical Trials

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THE desirability of properly timing and prolonging the purely sympomatic benefit which the newer antihistaminics afforded in reversible allergic disorders (notably urticaria and angioneurotic edema) soon became apparent. Accordingly, several drug manufacturers fulfilled a request to produce a four- to six-hour enteric-coated antihistaminic for clinical trial. Twenty-five mg. tablets of Thenylpyramine (N, N-dimethyl N'(2-thenyl)-N''-(2-pyridyl)-ethylenediamine) in this form were promptly furnished.* The average dose used was two tablets for adults and one for children.

The general subject of antihistaminic drugs has been thoroughly discussed previously,[1] and no new indications for the group can be added. The limitations imposed by the four- or five-hour effectiveness of the uncoated antihistaminics, however, suggested the following uses for the delayed action type:

1. The prevention of spontaneous allergic phenomena which regularly occur four to nine hours after retiring.
2. The prevention of delayed reactions from drugs, biologicals, immunizing allergens, et cetera, known to produce them between the effective time limits.
3. Prevention of nocturnal distress from willful ingestion of known food allergens.
4. Securing eight to ten hours of continuous action by the simultaneous ingestion of coated and uncoated antihistaminic drugs. This system can (a) eliminate mid-day doses for absent-minded, busy or sensitive people, (b) allow continuous relief throughout the night by bedtime dosage only, and (c) assure an allergist at least nine or ten hours of prophylaxis from constitutional reactions, without alarming the apprehensive patient.
5. Prevention of gastrointestinal disturbances produced by the uncoated drug.

Since the enteric-coated Thenylpyramine is pharmacologically no different from the uncoated, other than in its site and timing of absorption, it was tried only in cases in which the uncoated drug was known to be effective. The object was to test a method of administration only, for data on the type and percentage of cases benefiting was already known.[2,3] All subjects served, therefore, as their own controls. When nocturnal effectiveness was under investigation, the subjects had previously been roused by alarm clock to take the uncoated drug.

The results are shown in Table I.

*Supplies furnished through courtesy of Eli Lilly and Co.

TABLE I. RESULTS WITH PLAIN AND ENTERIC-COATED THENYLPYRAMINE

(A) Type of case	(B) Total cases	(C) Cases benefiting from uncoated drug	(D) Cases from Col. C in which enteric-coated drug tried	(E) Cases in which enteric-coated drug produced desired effect
Constant urticaria**	25	21 (84%)	21	21
Late night and early a.m. urticaria**	10	9 (90%)	9	7
Hay fever, seasonal	49	30 (61%)	28	26
Perennial allergic rhinitis	26	8 (30%)	8	6
Delayed reactions from injected allergens	25	23 (92%)	20	17
Gastrointestinal allergy (intentional ingestion)	16	5 (31%)	5	5
Nocturnal urticaria from afternoon injection of penicillin (Proc. or POB)	4	4 (100%)	4	3
Urticaria and local reaction from Globin Insulin	2	2 (100%)	2	2
Urticaria and local reaction from Protamine Zinc Insulin	2	2 (100%)	2	2
Asthma, seasonal	16	5 (31%)	5	4
Asthma, perennial	31	3 (9.7%)	3	2
	206	112 (54%)	107	95 (89%)
Gastrointestinal irritation from uncoated drug	19		19	16 (84%) prevented

**Many of the urticaria cases also had angioneurotic edema.

SUMMARY AND CONCLUSIONS

The uncoated Thenylpyramine afforded moderate to complete clinical relief or prevention of symptoms for 112 (54 per cent) of 206 allergic individuals. The enteric-coated drug, with a four- to six-hour delay in action, seemed theoretically indicated under certain circumstances listed above. It was accordingly tried on 107 of the aforementioned relieved group of 112, with prevention of symptoms in ninety-five (89 per cent); thus, the practicality of this mode of administration for procuring delayed action was verified.

Nausea and epigastric distress from uncoated Thenylpyramine are relatively slight compared to the other antihistaminic drugs in common use, occurring in nineteen of the 206 cases (9 per cent). (In only one-fourth of these was discontinuance necessary.) These symptoms in this group of nineteen patients were abolished in seventeen by the use of enteric-coated tablets, but the other usual side reactions to antihistaminic drugs were not diminished; they were merely made more difficult to identify. It is obvious that the uncoated tablets should always be tried first in order to allow such idiosyncrasies to be identified more easily.

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REFERENCES

1. Hartman, M. M.: The newer drugs for allergic disorders and their place in the histamine theory. California Med., 66:242, (April) 1947.
2. Lee, H. M.; Dinwiddie, W. G., and Chen, K. K.: The antihistamine action of N-(2-pyridyl)-N-(2-thenyl)-N′, N-dimethylethylenediamine hydrochloride. J. Pharmacol. & Exper. Therap., 90:83, 1947.
3. Pierce, J. D., and Mothersill, M. H.: Treatment of allergic symptoms with a new antihistamine drug. J. Indiana M. A., 40:739, 1947.

SENSITIVITY TO KELCOLOID
Preliminary Study

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THE COMMON water-soluble gums of importance, other than algin, are locust bean gum (Carob bean gum), karaya, acacia (gum arabic), tragacanth and Irish moss extract (carrageenin). Human hypersensitivity to these substances has previously been recognized and reported.[1,2]

Algin is the common name for designating alginic acid and its derivatives. Algin compounds are sodium alginate, potassium alginate and ammonium alginate.

Alginic acid is the hydrophilic colloidal polymer of anhydro-B-D-mannuronic acid that is extracted from various species of brown algae. It is primarily derived from giant kelp, Macrocystis pyrifera. Propylene glycol esters of fatty acids have previously been shown to have no significant toxic effects.[3] Propylene glycol itself is well tolerated in medicinal preparations used orally, parenterally, and as aerosols. Kelcoloid* is the propylene glycol ester of alginic acid (propylene glycol alginate).

Because of their hydrophilic colloidal properties, these algin products are used as thickening, suspending, stabilizing, emulsifying, gel-producing, film-forming, and adhesive agents in numerous food and industrial products. The alginates in general are utilized in ice creams, sherbets and ices, chocolate milk, cheeses, puddings, bakery goods, confectionaries, jellies and syrups, breads, pharmaceuticals, cosmetics, shampoos, shaving creams, toothpastes, paper coatings and sizings, adhesives, textile printing and sizing, water emulsion paints, boiler compounds, welding rod coatings, leather finishings, ceramics, insecticides, cleaning compounds, detergents, polishes, et cetera. Ammonuim alginate is used primarily in creaming and thickening natural and synthetic rubber lattices and rubber compositions, in water paints and wherever the presence of sodium is objectionable. Potassium alginate is most commonly used in dental impression compositions.

Kelcoloid, like other algin products, gives viscous aqueous solutions at relatively low concentrations. It is used as an emulsifying, thickening, stabilizing and suspending agent, in many food and industrial preparations. Unlike sodium alginate, it is soluble in acid solutions. It has pronounced emulsifying properties which make it excellent for use in acidic media such as flavor emulsions, French dressings and salad dressings. It is also used as a stabilizer and thickener for meat sauces, meringues, syrups and toppings. It is found in certain pharmaceutical and industrial products such as medicinal jellies, mineral oil emulsions, industrial polishes and cleaning compounds.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*Manufactured by the Kelco Company of San Diego.

METHOD OF STUDY

An attempt has been made to study possible human hypersensitivity to Kelcoloid, and investigations were carried out in the following manner: Fifty individuals known to be allergic to numerous inhalants and foods were tested intradermally to various dilutions of Kelcoloid. As a control, fifty individuals without an allergic history and without a familial history of allergy were also tested.

Individuals giving skin reactions considered to be significantly positive were tested by the indirect (passive transfer) method. In those instances where direct and indirect positive skin tests were obtained, the patients were fed varying amounts of the preparation in order to note the clinical effect.

The results of the skin reactions of both groups of individuals are shown in Table I.

TABLE I

Allergic Individuals				
+ — (Irritative) 5 cases	+ Very Slight 6 cases	+ + Slight 3 cases (1—delayed)	+ + + Moderate 2 cases	+ + + + Severe None
No reaction—33 cases				

Nonallergic Individuals				
+ — (Irritative) 7 cases	+ Very Slight 3 cases	+ + Slight None	+ + + Moderate None	+ + + + Severe None
No reaction—40 cases				

It will be noted that no severe skin reaction occurred in either the allergic or the nonallergic group. Moderate reactions occurred in two cases in the allergic group, and none in the nonallergic group. Slight reactions occurred in three cases in the allergic group, one being a delayed reaction, and none in the nonallergic group. Very slight reactions occurred in six allergic individuals and in three cases in the nonallergic group. Irritative reactions occurred in a total of twelve cases.

Of the allergic group, five persons giving significantly positive skin reactions (slight to moderate) were tested by the indirect method. These gave positive passive transfer tests. Three of these individuals, when fed amounts of Kelcoloid somewhat greater than would normally be ingested as food, reproduced their usual allergic manifestations to a mild degree. This occurred each time the preparation was administered.

CONCLUSIONS

The results of sensitivity studies on Kelcoloid indicate that only a very small percentage of the allergic population shows evidence of clinical sensitivity. No significant sensitivity could be demonstrated in a group of

(Continued from Page 718)

OBSERVATIONS ON THE ACTION OF ORTHOXINE IN PATIENTS WITH BRONCHIAL ASTHMA

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SINCE the majority of sympathomimetic drugs now in use for the symptomatic relief of asthma are associated with a relatively high incidence of undesirable side reactions, current efforts in the development of new antiasthmatic drugs are being directed toward the synthesis of bronchodilator substances which lack strong vasopressor action and central nervous system-stimulating effects. One recent development along these lines is the n-isopropyl amine derivative of epinephrine (Isuprel), which not only divorces bronchodilator action from pressor effect but is associated with a strong vasodepressor response.[5] This compound, however, also presents certain limitations in its clinical use. Its oral action is questionable, and when injected it is frequently accompanied by profound stimulation of the heart and a precipitous fall in blood pressure. The most satisfactory clinical application of this drug has been by inhalation.[7] A more recent development which shows considerable promise, is the synthesis of the orally active drug, Orthoxine* (ortho-methoxy-B-phenyl-isopropyl methylamine hydrochloride). In the experimental animal this drug is more effective than ephedrine in relieving bronchoconstriction; it induces practically no pressor response, effects less central nervous stimulation, and has no greater toxicity than ephedrine when administered orally.[6] Curry, Fuchs, and Leard[1] have found the drug effective by mouth in bronchial asthma and in asthma-like attacks induced by the parenteral injection of histamine and methacoline. Wittich[8] observed a beneficial effect not only in asthma but in some cases of seasonal hay fever and allergic headache.

The following observations were made in a group of ambulatory patients with chronic asthma, all of whom had been followed for some period of time in the out-patient clinic or in private practice. Orthoxine was administered orally in these patients, and its effect was noted on symptoms of asthma, vital capacity, pulse and blood pressure. Since all of these individuals were taking or had taken ephedrine for symptomatic relief in the past, an effort was made to elicit any history of intolerance to this drug. An accurate comparison with the effects of Orthoxine could therefore be made, especially in those who had experienced rather profound side reactions from small doses of ephedrine.

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*Orthoxine was supplied for this study by the Research Division, The Upjohn Company, Kalamazoo, Michigan.

TABLE I. EFFECT OF ORTHOXINE ON VITAL CAPACITY OF ASTHMATIC PATIENTS

Patient	Dose mg.	Degree of Asthma (mild—mod.—severe)	Vital Capacity in c.c.					Symptomatic Effect (excellent—good—fair—negative)
			Before	After				
				15min.	30min.	45min.	60min.	
J.G.	100	Moderate	2200	2400	2600	2600	2600	Good
F.R.	100	Moderate	2600	2400	2600	2600	2600	Good
W.P.	100	Moderate	2000	1800	1800	1600	1800	Negative
R.E.	100	Mild	2400	2600	2800	3000	3000	Excellent
S.G.	100	Moderate	2200	2600	2400	2200	2200	Fair
J.S.	200	Moderate	1600	1800	2200	2200	2200	Negative
M.M.	200	Moderate	2200	2800	2800	2800	2800	Excellent
N.W.	200	Severe	1800	1000	1200	1800	1800	Negative (required i.v. aminoph.)
E.O.	200	Severe	1800	1800	2200	2600	2600	Excellent
P.W.	200	Moderate	2000	1800	1800	2000	2000	Negative
F.K.	200	Severe	1000	800	1200	1200	1400	Fair
R.E.	200	Mild	2400	2000	2000	2800	2800	Good
C.N.	200	Severe	1000	1000	800	——	——	Negative (required i.v. aminoph.)
G.M.	200	Moderate	2400	2400	2400	3000	3000	Excellent

VITAL CAPACITY

The effect of Orthoxine on vital capacity was observed in fourteen ambulatory patients who presented themselves in the office or out-patient clinic with symptoms of asthma. Determinations were made with the McKesson-Scott apparatus prior to the ingestion of 100 to 200 mg. of Orthoxine, and at fifteen-minute intervals during the next hour. Auscultation of the chest was carried out before and after the drug was taken, and the degree of asthma classified as mild, moderate, or severe (Table I).

An increase in vital capacity was recorded in nine cases during the period of observation. All but one of these patients experienced a favorable symptomatic effect. Vital capacity readings were unchanged or slightly decreased in five other subjects during the one-hour period following ingestion of Orthoxine. One of these patients obtained symptomatic improvement despite failure to show an increase in vital capacity, while the remaining four required other measures to relieve their asthma. Two responded to inhalations of Isuprel, and two required intravenous aminophylline. The findings on chest examination before and after Orthoxine in most instances paralleled the recorded changes in vital capacity.

CARDIOVASCULAR EFFECT

The effect of Orthoxine on the cardiac rate and blood pressure was noted in eighteen asthmatic patients. Observations were made before the drug was administered and at regular intervals for one hour following its ingestion (Tables II and III).

An increase in pulse rate of 10 beats per minute or more was recorded in six subjects; a decrease of the same degree occurred in three subjects; variations in the remaining nine cases were less than 10 per min-

TABLE II. EFFECT OF ORTHOXINE ON PULSE RATE

Patient	Dose mg.	Resting Pulse	Pulse After Orthoxine			
			15 min.	30 min.	45 min.	60 min.
I.M.	100	72	92	88	88	84
L.G.	100	60	60	60	60	60
S.W.	100	72	72	72	80	72
H.T.	100	90	82	88	88	88
M.G.	100	81	88	84	76	76
S.L.	100	112	101	100	96	96
L.S.	100	88	88	88	88	88
G.S.	100	72	78	72	72	72
I.G.	100	78	78	78	78	78
F.R.	100	72	78	72	72	84
J.S.	200	102	96	120	120	120
M.M.	200	114	102	108	102	102
N.W.	200	84	72	90	84	84
E.O.	200	78	88	86	84	84
W.P.	200	108	108	120	112	112
R.E.	200	112	108	100	108	108
F.W.	200	108	116	120	120	120
C.N.	200	120	116	120	120	120

TABLE III. EFFECT OF ORTHOXINE ON BLOOD PRESSURE

Patient	Dose mg.	Resting Blood Pressure	Blood Pressure After Orthoxine			
			15 min.	30 min.	45 min.	60 min.
I.M.	100	130/70	118/68	120/70	120/70	120/70
L.G.	100	142/80	121/70	118/60	124/65	130/70
S.W.	100	120/80	110/80	104/76	115/80	115/80
H.T.	100	102/60	100/60	98/64	96/60	100/60
M.G.	100	142/90	130/90	130/90	130/90	130/90
S.L.	100	110/80	110/80	108/80	110/80	110/80
L.S.	100	150/110	151/106	160/104	154/110	154/110
G.S.	100	190/98	160/91	144/90	160/96	160/94
I.G.	100	110/66	110/61	110/64	110/66	110/64
F.R.	100	168/98	151/91	128/90	120/89	132/80
J.S.	200	172/120	180/120	172/120	164/120	170/120
M.M.	200	148/110	158/104	140/100	144/104	144/110
N.W.	200	112/80	104/80	108/80	104/80	104/80
E.O.	200	104/80	96/80	100/80	98/80	96/80
W.P.	200	122/100	122/90	120/86	100/80	100/80
R.E.	200	110/60	96/60	100/60	100/60	100/60
F.W.	200	100/70	88/62	82/58	94/62	96/62
C.N.	200	100/70	100/70	100/70		

ute. In no instance did the change in pulse rate exceed 20 beats per minute.

A fall in systolic blood pressure of 10 to 44 points was recorded in nine subjects, associated in five cases with a decrease in the diastolic level of from 10 to 20 points. The greatest drop occurred in those with abnormally elevated readings prior to ingestion of the drug. An increase of 10 points in the systolic pressure was recorded in only two subjects. No significant increase in diastolic pressure occurred. In two cases there was a slight increase in pulse pressure.

ANTIHISTAMINIC ACTIVITY

This phase of action was briefly investigated on the basis of Wittich's report that some patients with hay fever and allergic headache were benefited by Orthoxine.[8] Guinea pigs which were given 100 to 200 mg./kg. of the drug intraperitoneally failed to survive one lethal dose of histamine administered intravenously fifteen minutes later. Inhibition of histamine

wheaing in normal human skin, as determined by techniques developed for the assay of antihistaminic drugs,[3] was negligible. It would appear, therefore, that antihistaminic activity of Orthoxine, if present, is not of the same order shown by the so-called "antihistaminic drugs."

CLINICAL EFFECT

Sixty-one patients with asthma were given 100 mg. tablets of Orthoxine. They were advised to take one as necessary for the relief of difficulty, and to repeat the dosage at four-hour intervals if symptoms recurred. Thirty-seven of these reported symptomatic improvement beginning within five to thirty minutes after ingestion of the drug, and lasting for at least one hour, and in some cases for as long as twelve hours. Twenty-four patients obtained no relief following the use of the drug in doses of 100 mg. Six of these experienced a good symptomatic effect when the dose was increased to 200 mg. In twenty-four additional patients, a dose of 200 mg. produced a good response in nineteen, while five others reported no improvement. In those who continued to use Orthoxine over a period of time for symptomatic relief, it was noted that mild or moderate attacks usually responded quite well to the drug, while unusually severe asthma frequently required measures beyond orally ingested medication for relief.

SIDE EFFECTS

Fifteen patients in the group of asthmatics who were given Orthoxine were known to be extremely intolerant to small doses of ephedrine. Ephedrine and ephedrine-like drugs usually produced in these patients symptoms such as nervousness, insomnia, tremor, vertigo, headache, and palpitation. Twelve of the fifteen were able to take 100 to 200 mg. doses of Orthoxine without experiencing such effects. Three others reported relatively mild symptoms of central nervous system stimulation. One of these experienced such effects only from 200 mg. doses and was able to tolerate 100 mg. amounts very well. In the entire group of eighty-six patients who received Orthoxine, nausea was reported in eight cases following large doses of the drug taken on an empty stomach. In some instances this was not present when the dose was reduced to 100 mg. or when it was taken immediately after meals. One patient reported a "choking sensation" with increase of asthma following ingestion of the drug.

DISCUSSION

In developing new sympathomimetic drugs which divorce bronchodilator action from pressor effect, it should be recalled that both of these characteristics are probably important as far as the relief of the asthmatic paroxysm is concerned. The action of epinephrine on the bronchial tree is twofold: first, relaxation of the bronchial musculature, and second,

vasoconstriction with reduction in the swelling of the mucosa. The latter is very likely as important as bronchodilation in affording relief in asthma. Very frequently, however, vasoconstriction is followed by a prolonged inhibitory phase, with vasodilatation and congestion of the mucosa, and may very likely be related to the "epinehrine-fastness" so frequently encountered in severe asthma. Such "after-congestion" is also seen in the nasal mucous membrane following the use of epinephrine as well as other strong local vasoconstrictors.[2] With epinephrine, this effect may be related to the vasodilator component of its action, but in the case of other strong vasoconstrictors it appears that another mechanism, probably a compensatory reaction, is involved. The constrictor effect of ephedrine on arterioles is less marked than that of epinephrine, and a vasodilator component in its action is not demonstrated. An increase in pulse rate, blood pressure and cardiac output is usually associated with its clinical use. Patients with hyperthyroidism and hypertension may be more sensitive to its action than normal persons. Ephedrine influences respiration in two ways: by bronchodilation and by direct stimulation of the respiratory center. In addition, however, it is a strong central nervous system stimulant, which accounts for the majority of its side effects.[1]

Orthoxine affords relief in bronchial asthma principally through its bronchodilator effect, which from experimental studies is found to be considerably greater than that of ephedrine. Clinically, a 100 mg. dose of Orthoxine produces a response in asthma approximately equivalent to that of a 25 to 50 mg. dose of ephedrine. The effectiveness of the smaller amount of ephedrine is very likely the result of vasoconstriction and respiratory stimulation added to its bronchodilator action. The larger dose of Orthoxine, however, is often clinically effective without producing the undesirable side effects which so frequently accompany the use of ephedrine. Its minimal effect on cardiac rate, and the lack of pressor response, would indicate that Orthoxine is a desirable drug in the asthmatic patient with hypertension or other cardiovascular disease. The relative infrequency of central nervous system stimulation allows its use in many who are unable to employ other orally effective agents for the relief of asthmatic symptoms.

SUMMARY

1. Orthoxine (ortho-methoxy-B-phenyl-isopropyl-methylamine hydrochloride) is a new, orally effective, synthetic bronchodilator substance, whose action is not associated with strong vasopressor activity or central nervous system-stimulating effects.

2. The average orally effective adult dose of Orthoxine is from 100 to 200 mg. An increase in vital capacity frequently follows this amount of drug, while relatively little alteration in cardiac rate is seen. A slight drop in systolic blood pressure, more pronounced in those with hypertension, may occur.

3. Side effects from Orthoxine are mild and relatively infrequent. Many patients who are extremely intolerant to ephedrine are able to take a clinically effective dose of Orthoxine without difficulty. Nausea and mild central nervous system-stimulating effects are occasionally seen.

4. The clinical effectiveness of Orthoxine in bronchial asthma, its lack of pressor action or cardiac and central nervous system stimulation, suggests its use in place of ephedrine, especially where hypertension, cardiovascular disease and side effects preclude the use of ephedrine.

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REFERENCES

1. Curry, J. J.; Fuchs, J. E., and Leard, S. E.: Clinical and experimental studies with Orthoxine in the treatment of bronchial asthma. J. Allergy, 20:104, 1949.
2. Feinberg, S. M., and Friedlaender, S.: Nasal congestion from frequent use of Privine hydrochloride. J.A.M.A., 128:1095, 1945.
3. Friedlaender, A. S., and Friedlaender, S.: Correlation of experimental data with clinical behaviour of synthetic antihistaminic drugs. Ann. Allergy, 7:83, 1949.
4. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York: Macmillan Company, 1941.
5. Lands, A. M.; Nash, V. L.; Dertinger, B. L.; Granger, H. R.; and McCarthy, H. M.: The pharmacology of compounds structurally related to hydroxytyramine. J. Pharmacol. & Exper. Therap., 92:369, 1948.
6. Research Laboratories, The Upjohn Company, Kalamazoo, Michigan: Personal communication.
7. Segal, M. S., and Beakey, J. F.: Management of bronchial asthma: the use of 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol. Ann. Allergy, 5:317, 1947.
8. Wittich, F. W.: A clinical evaluation of Orthoxine in the treatment of allergic disease. Ann. Allergy, 6:664, 1948.

THE USE OF BACTERACIN, A NEW ANTIBIOTIC IN AEROSOL FORM

(Continued from Page 675)

7. Meleney, F. L., and Johnson, B.: Bacitracin therapy; the first hundred cases of surgical infections treated locally with the antibiotic. J.A.M.A., 13:675, (Mar. 8) 1947.
8. Meleney, F. L.; Altemeier, W. A.; Longacre, A. B.; Pulaski, E. J., and Zintel, H. A.: The results of the systemic administration of the antibiotic, bacitracin, in surgical infections; a preliminary report. Am. Surg., 128:714, (Oct.) 1948.
9. Prigal, S. J.; McGavack, T. H., and Bell, M.: The effect of propylene glycol on the antibiotic activity of human serum. Am. J. Med., 3:185, (Aug.) 1947.
10. Prigal, S. J.; Morgenbesser, L. J., and McIntyre, F. P.: Penicillin aerosol in the prevention and treatment of respiratory infections in allergic patients. J. Allergy, 18:325, 1947.
11. Prigal, S. J.; McGavack, T. H.; Speer, F. D., and Harris, R.: Aerosol penicillin: blood levels of penicillin obtained by inhalation of aerosols produced by a combined steam generator and aerosolizer with the use of propylene glycol, tents and a breathing box. J.A.M.A., 134:932, 1947.
12. Prigal, S. J.: Further observations on the prevention and treatment of respiratory infection in allergic patients. J. Allergy, (to be published).
13. Prigal, S. J., et al: Streptomycin blood levels (To be published.)
14. Smith, L. W.: Personal communication.
15. Smith, L. W.: In vitro studies on possible synergistic action between penicillin and bacitracin. (Unpublished data.)

Progress in Allergy

HAY FEVER
A Review of the Literature of 1948

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Although a considerably larger number of articles on this subject appeared in the world's literature in 1948 than those upon which we reported last year,[105] we regret that basic advances of note were lacking. Dan Campbell[37] stated that he "cannot help but feel that many of the underlying causes of hypersensitivity reactions in man are intimately associated with phenomena of immunity, and that an immunochemical approach to the problem of allergy is of fundamental importance." In turn, we cannot help but subscribe to these feelings.

BOTANY AND POLLEN SURVEYS

O. C. Durham's[50] report on airborne allergens in the National Parks reveals an intensive study of the pollens found during the period the parks are open to the public. Many are ragweed free or are relatively so. Among those free are Bryce Canyon, Glacier, Grand Canyon, Grand Teton, Isle Royale, King's Canyon, Mt. McKinley, Mt. Rainier, Olympic, Sequoia, Yellowstone, and Yosemite National Parks.

Targow,[175] reporting on a pollen survey of the Los Angeles area over a five-year period, notes that pollen counts are relatively low when compared to the Midwest; however, the seasons are more prolonged and overlapping. Trees pollinate intermittently from January to November; grasses pollinate in March, reach a peak late in May or early June, then gradually decline to about mid-December. Weeds begin with chenopods and amaranths in March, followed by ragweeds in April and artemesia in June. Peaks reached by ragweeds are minimal in May and maximal from August to October, followed by artemesia in September, October and November.

Deppe,[54] in a discussion of the hay-fever pollens in the Seattle area, notes that there are no ragweeds west of the Cascade Mountains. The Cascade Mountains are a natural barrier and divider for the variation in pollens found in the upper northwestern part of the United States. The two main tree pollens are the alder in April and the willow in May. Other offenders are: hazel, maple, ash, birch, elder, dogwood and poplar. The grasses which pollinate from mid-May to July are: june, orchard, stallion, and perennial rye, velvet, timothy and red top. The weeds pollinate from July to frost. The chief offenders are: plantain, sheep sorrel, pigweed, lamb's quarter and curly dock.

Shure and Harris,[164] of Los Angeles, point out that ragweed pollen cases will be in trouble in southern California from western ragweed, burr ragweed and slender ragweed pollen. Furthermore, the ordinary grass-and-weed case of the East will sooner or later in southern California have hay fever from February through November.

Wine,[187] in discussing the "X-Hay Fever Problem in the South," stated that it is limited to the middle of South Carolina, the southern two-thirds of Georgia, Alabama, northern Florida, the western tip of Tennessee, Mississippi, Louisiana

and southeastern part of Texas. The offending agent is present in the air from May to October. Complete relief is obtained when the affected individual leaves the area or goes to the seashore.

Wolf,[193] reporting on a fall-pollinating red berry juniper, finds this tree distributed over parts of central and west Texas, southwestern Oklahoma and southeastern Arizona. It has been identified as Juniperus pinchoti (Sudworth), or red berry juniper. It closely resembles J. ashei, but it pollinates from the latter part of September to early in December and is introducing another pollen season in the areas involved. The cedar promises to become more profuse and more widespread due to the fact that it regenerates from roots and cannot be killed above the ground. It is similar antigenically to J. ashei and is a significant cause of hay fever.

E. H. Walzer, Siegel, Chait and M. Walzer,[184] in their second series of surveys of ragweed pollination in Greater New York Metropolitan District, include localities within a 50-mile radius of New York City. The technique employed was approved by the Pollen Survey Committee of the American Academy of Allergy. The pollen density in this area was comparatively low in 1947. The highest seasonal total count for the city was obtained at the Staten Island station. The remaining city stations listed in the order of decreasing pollen density were as follows: Flushing, Manhattan, Rockaway, Jamaica, Bronx, and Brooklyn. Three peaks in the pollen season were noted at most of the stations included in the survey. The first occurred during the last week in August; the second, which was the greatest, during the first week of September, and the third during the second week of September. Because of the relatively light pollen season, the influence of the ragweed extermination program on the ragweed counts, in this city, could not be evaluated.

Claus,[41] in a study of the anemophilous plants of Puerto Rico, found that some wind-pollinated species are similar to those found in the United States. Marchand[124] reports on hay-fever plants of Puerto Rico, and says that pollinosis does occur in Puerto Rico from grasses and amaranths. Bermuda grass is found from November to February. The chief amaranth offender is spiny amaranth. Sugarcane pollen is found all year around. Trees are present, but pollen from the Australian pine is the only one suspected. Artemesia are rare.

Gottlieb,[79] discussing a note appearing in the *JAMA* on the book notice of "Diseases of Children," edited by Patterson of England, found nothing surprising in the statement that "nothing is said about hay fever caused by giant and dwarf ragweed, or about desensitization against this type." Ragweeds generally do not exist in the British Isles, and in fact are of no practical consequence in Europe. The only significant hay fever in Britain is that due to pollens of grasses.

Alford,[9] discussing allergy in Japan, indicates that it is in striking contrast to allergy in the United States. The climate and general topography of the country are such that grasses and ragweeds are not important factors in the causation of allergic symptoms. No records of seasonal hay fever were noted. Fifteen per cent of the land is under cultivation, and 50 per cent of the cultivated land is in rice. Fifty per cent of the land is forest with oak, ash, birch, elm and poplar predominating.

Greco and Bartos,[80] in a pollen survey in the air of the city of Santos, Brazil, found pollen present from June to September. The most common pollen is grass, of the variety of *Melinis minutiflora*. The total pollen count was very low.

Heise and Heise,[93] report on the distribution of ragweed pollen and Alternaria spores in the upper atmosphere. Counts of ragweed pollen and Alternaria spores in the upper atmosphere were made during flight. The greatest concentration of pollen occurred at 3500 feet. Cumulus clouds and surrounding atmosphere

contained many times the number of particles found in clear air away from the clouds. The level of maximum concentration of particles rose from early afternoon to 8:00 p.m., when it fell slowly until dawn.

Rooks[151] describes a device for the electrostatic precipitation of pollen and fungus spores upon a counting slide. This electrostatic precipitator is portable, and can sample volumetrically airborne pollen and fungus spores by the slide method and with additional essential instruments it is possible to determine the incidence of airborne bacteria and fungus spores by the culture plate method. This electrostatic precipitation, in which special glass slides with conducting surfaces are used with the prescribed instrument, offers a convenient, efficient and new approach to certain experimental problems involving airborne pollen and fungus spores.

Alemany-Vall[6] discussed rhinitis and asthma caused by pollen in Barcelona. The author made a definite attempt to find the etiological agent which is responsible, on the basis of the skin tests as well as surveys of the patients' surroundings. Many species of gramineous pollen were examined. These species were all found within the municipal boundaries of Barcelona from March to July. The pollen of Parietaria officinalis is a frequent cause of simple and complicated rhinitis after asthma. The scarcity of pollenosis asthma not preceded by pollenosis rhinitis due to the plant is discussed. Studies of hay fever showed that the nasal mucous membranes were red and irregularly swollen, even in old and stationary cases.

Blumstein[21] discussed the ragweed extermination plan of Philadelphia for the year 1948. The chemical 2,4-D (dichlorothenoxyacetic acid) was used. The plan was publicized in all newspapers and the health department notified of areas which were high in ragweed, and the trucks were then sent out to spray. The program was partially successful.

In 1946 the health department of Brooklyn had such a program and met with similar success. An interesting note on the Philadelphia study was the report of the pollen count of eight stations in different sections of the city. The pollen counts in these sections varied considerably. This is not an infrequent observation by many investigators who count pollen from different sections of a single city.

C. Juhlin-Danfeldt,[103] in an excellent article, reviewed the pollen situation of the northern countries of Europe. There are two hay-fever seasons in Sweden. The spring season is due to the trees, namely, Pinus, as well as Betual, Picea, Populus, Onecus, Juniperus, Anlus; the grass season occurs in the summer. There is a small amount of weeds belonging to the artemesia family. The patients are usually tested with birch pine, timothy, English plantain, sheep sorrel, lambsquarters, linden, oxeye daisy, and common mugwort. Of the people who are sensitive, 29 per cent are due to trees, 76 per cent due to grass, and 16 per cent due to the compositae. Treatment with the tree extracts in dilution of 1:10,000 to 1:1,000 are used, and grass extract in dilutions of 1:10,000 to 1:100,000 are used. The preseasonal and the coseasonal methods are the ones of choice.

FUNGI

A number of investigators have been studying the relationship of molds in outdoor air and indoor air. Newton, Scherago and Weaver[135] studied the mold distribution in outdoor air, indoor air and house dust, in eastern, central and western Kentucky. They found seasonal variations, with penicillium and phycomyces predominating. Some differences were noted in the various sections of the state, but were slight. Four genera previously not reported were encountered, namely, montospora, stemphylium, tetra-coccosporum, and phycomyces. Their observation that certain molds occur predominately in outdoor air, and others in house dust, points to their suggestion of including house dust, as well as air, in surveys of mold distribution.

Flensborg and Samsoe-Jensen,[71] using Feinberg's technique, cultured the outside air for mold spores by counting the number of colony growths on a five-minute exposure of a Petri plate. Marked variations in mold counts were noted. Hormodendrum was first noted in June, and it continued throughout the summer. Eighty to 120 colonies was the average count. Hormodendrum averaged 72 per cent of all colonies counted. Penicillium (9 per cent) was in the air during April and May. Alternaria (2 per cent) was at its height in August, and Pullularia (27 per cent) in July.

Flensborg and Samsoe-Jensen[72] reported on mold spore counts in Copenhagen during March to August, 1947. They found that Hormodendrum was highest, followed by Penicillium, Monilia, Pullularia, and Alternaria. Of the total number of spores counted, Hormodendrum was equal to 72.4 per cent, Penicillium 9.2 per cent, Monilia 2.4 per cent, Pullularia 2.2 per cent, and Alternaria 2 per cent. The predominant molds found indoors were of the genera Penicillium.

Ivar Nilsby,[71] discussing Flensborg's paper, reported on his results of mold spore counts of outdoor air compared to indoor air in Örebro. In outdoor air, Hormodendrum represented 68 per cent, Penicillium 11 per cent, Pullularia 6 per cent, yeast 3 per cent, Botyritis 1.5 per cent, and Aspergillus 1.3 per cent. In the indoor air Penicillium represented 43.5 per cent, Hormodendrum 27.5 per cent, yeastlike organisms 10 per cent, Aspergillus 6.2 per cent, Pullularia 5.6 per cent, Mucor 2.8 per cent, Alternaria 2.1 per cent, and miscellaneous 1.2 per cent.

M. Schwartz,[71] continuing the discussion of Flensborg's paper, reported that he cultured fungi from house dust. Among the varieties found, Penicillium was first, with 117 colonies; the others found were Aspergillus with 36 colonies, Mucor 29 colonies, Alternaria 19 colonies, Fusarium 15 colonies, Rhizopus 5 colonies, and Hormondendrum 3 colonies. From a simple house dust specimen, seven varieties of fungi were cultured, from which extracts prepared gave only two positive skin tests in the patient from whom the dust was obtained.

Reymann and Schwartz[147] reported on their studies of the occurrence of allergenic fungi found in house dusts for twenty-two Danish asthmatic patients. Their results were similar to the above studies in the variety and distribution of fungi. Six of the twenty-two gave positive cutaneous reactions to one or more of the fungi. Thirteen of twenty-two patients showed positive cutaneous reactions with autogenous house dust extracts, and five of thirteen had positive reactions to fungi cultured from their dust. In nine patients in whom autogenous house dust extracts were negative, one was positive to the fungi cultured from the dust. This would indicate that although there is no common antigen, one should test with extracts of fungi cultured from their house dust as well as the house dust itself.

Eisenstadt[62] reports that the dominant molds in the Minneapolis area are Alternaria, Hormodendrum, Helminthosporium, Aspergillus, Penicillium, Fusarium, Phoma, Mucor, Mycogene, and Pullularia; except for Penicillium and Aspergillus molds, they have a seasonal variation, becoming relatively few in the winter and profuse in the summer. Of 246 patients tested with eight different molds, and 124 tested with Alternaria and Hormodendrum, there were 34 per cent positive reactions (36 per cent tested with eight molds, and 33 per cent tested with Alternaria and Hormodendrum). Age incidence is similar to pollens, and multiple sensitivity is the rule. The tests were clinically significant in 29 per cent of the patients and of primary etiological importance in 11 per cent.

POLLEN PURITY

With the recommendations of Dr. Veldee,[180] of the United States Public Health Service, for the collection and preservation of pollens becoming accepted by the men

interested in collection and selling, as well as by the two national organizations interested in allergy, it is hoped that a start in the direction of standardized allergenic materials has been made. These specifications are listed under the headings, "Qualifications of the Pollen Collector," "Labelling the Dispensing Container," "Purity of the Pollen," "Stability of the Active Component of the Pollen," "Type of Container," "Changes of Color in the Dry. Pollen," "Co-operation of the User," and "Collections of Pollen." No reports have appeared in this year's literature of gross contamination or mislabelling of pollens. It has been noted by many that different lots of the same type of pollen, collected in different localities, have different potencies when extracted by the same method. The potencies vary in their nitrogen content, protein nitrogen content, and in their biological skin activity.

IMMUNOCHEMISTRY

In past years, much knowledge in the field of allergy was stimulated by the active workers in the field of immunochemistry. It seems that since the rebirth of psychodynamics, basic investigations in allergy have been somewhat stifled. It is, therefore, with a great deal of regret, that the authors find little of noteworthy progress in this particular branch of allergy.

Wodehouse[102] reports interesting observations on patterns of allergic sensitization. Clinically, pollen-allergic patients of the multiple sensitization type generally have a single major sensitization upon which the others all depend. The pollen atopen has a mosaic structure similar to that found in the bacterial or animal cell, and is susceptible to analysis. It consists of a major antigen which is species-specific or group-specific, being shared, if at all, only by the phylogenetically closely related species. It has also a number of minor antigens which are common to the related and unrelated species in an unpredictable way. The minor antigens are capable of producing clinical symptoms.

Brown and Loveless[30] investigated the allergenic skin activity of low ragweed pollen after the extract was irradiated with ultraviolet light. One portion of a low ragweed extract was subjected to irradiation at 6 inches through a glass barrier for one hour, and another portion for thirty minutes. Both were compared with an untreated extract on ragweed-sensitive patients. The concentration of extracts which elicited threshold responses were compared. Cross neutralization studies were also made. It was noted that irradiation of low ragweed extract with the doses of ultraviolet light employed had no effect on the cutaneous reactivity of the extract.

Alexander, Johnson and Bukantz[7] studied the correlation between symptoms of ragweed hay fever and the titer of thermostable antibody. They find that there is a general lack of correlation of the above, as determined by the methods used and the degree of clinical protection afforded. The mechanism by which clinical improvement occurs following specific pollen therapy, remains unknown.

Hampton, Bukantz and Johnson,[87] in their studies on the deterioration of ragweed pollen extracts as measured by precipitation, neutralization and protein nitrogen analysis, with special reference to the prevention of deteriorization by glycerine. noted that glycerinated ragweed extracts showed no loss or less loss of activity than plain extracts after heating or storage at four different temperatures. Plain unglycerinated low ragweed extracts, upon heating to 56° C. for thirty minutes, and upon storage at room temperature, 6° C., minus 25° C., and minus 70° C. for periods up to one year, showed loss of activity as measured by their ability to precipitate anti-ragweed rabbit serum, and to neutralize skin-sensitizing antibodies of ragweed-sensitive human serum.

Bukantz, Johnson and Hampton[32] studied absolute colorimetric methods in the analysis of factors influencing precipitation of ragweed pollen extracts and homol-

ogous rabbit antisera. They used the quantitative microprecipitin technique of Heidelberger and MacPherson in the analysis of factors influencing precipitation of ragweed extracts and rabbit anti-ragweed serum. Refrigeration for forty-eight hours carried the precipitation to completion. There was least avidity of ragweed extract for rabbit anti-ragweed antibody in the region of considerable antibody excess. Striking differences were noted for two ragweed extracts in the relation between their protein nitrogen content and the total nitrogen precipitated from a single rabbit serum. The precipitinogenic activity of ragweed extracts diminished progressively during storage in the frozen state. A few preliminary experiments described the effect of "blocking" antibody upon this precipitating system. Normal serums were found to possess some inhibitory activity but much less than that observed with sera from treated ragweed subjects. The degree of inhibition by normal serum was unaffected by altering the conditions of precipitation in a manner which increased the effect of serum from treated ragweed subjects. A given amount of serum containing "blocking" antibody appeared to "neutralize" a fixed amount of antigen independently of the antigen-antibody ratio of the precipitating mixture. The significance of these observations is discussed.

Robbins, Samuels and Mosko[148] report their chemical studies on a skin reactive fraction from short ragweed pollen, which was prepared by utilizing the following principles: (1) heating at pH 4.0-4.1, (2) adsorption on $Al(OH)_3$ cream, (3) release by a pH 7.4 M/15 phosphate buffer, and (4) precipitation by alcohol at 0° C. The substance obtained by this method is head stable and skin reactive. The substance contains a protein component. Fourteen amino acids were quantitatively determined in fraction AA. The substance contains a carbohydrate component. It is a polysaccharide containing hexose, pentose, hexuronic acid, but no hexosamine. Spectrophotometric analysis in the ultraviolet showed the presence of small amounts of a flavanol pigment. This substance is more skin reactive than whole ragweed pollen solutions of the same nitrogen concentration. The skin-reactive principle is a protein-carbohydrate complex.

Suer[173] reports and discusses a chemical concept of immunity. Isocyanide structure is offered as the chemical characteristic of toxin; an amine derived therefrom, as antitoxins; the amidines resulting from combinations of the two, as immune body. The organic cyanides were likened to carbon dioxide, as the isocyanides were likened to carbon monoxide. Attention was called to several additional reactions of the isocyanides other than those of amines. An isocyanide as antigen, its derived amine as antibody, and the amidine as immune body, were made in the laboratory and tested for toxicity on mice. The outcome confirmed the expected. Chemical tests made upon E. C. Rosenow's streptococcal antigen and antibody gave evidence that the former contains isocyanide, and the latter, amine. A substance with properties typical of an amine hydrochloride, and highly agglutinative, was crystallized from Rosenow's antibody. A short series of simple amine hydrochlorides were tested for antibody properties. Of the group, methylamine and ethanolamine hydrochlorides were found to be less toxic and to exhibit the highest agglutinative power.

B. Campbell[36] reports on the inhibition of anaphylactic shock by acetylsalicylic acid. The author also used Benadryl, which gave good protection against histamine shock but was without effect on anaphylactic shock. He concluded that acetylsalicylic acid is a true anti-anaphylactic drug in that it interferes with the antigen-antibody reaction to prevent or to decrease the untoward results of the challenging dose of antigen.

Scrafini and Biozzi[161] studied blood histamine and histamine blood equivalents after physical exercise in normal patients and patients with hay fever. No significant changes of blood histamine were observed in normal subjects after physical exercise. In patients suffering with asthma and hay fever there was an increase of blood

histamine five to ten minutes after physical exercise. The appearance of allergic manifestations after physical exercise in patients suffering from hay fever, together with a definite rise of blood histamine, seems to suggest that blood histamine has a significant role in allergic reactions produced by physical exercise.

STANDARDIZATION

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Salen,[151] also a European, reviewed the entire problem of skin testing and biologic assay.

Walzer and Golan[183] evaluated the electrophoretic method of skin testing. The method was investigated with a special small type electrode, a current density of 0.5 milliamperes, a three-minute exposure and two drops of a 0.1 mg. nitrogen ex-

tract applied to the positive pole. With the above technique, antigen applied at the positive pole produced positive reactions in 86 per cent of the cases as well as 71 per cent who developed reactions simultaneously at the negative pole. With saline solution, no reactions occurred at either pole. When antigen was applied to the negative pole, 33 per cent of the cases developed positive reactions, but none developed simultaneously at the positive pole. The authors did not find electrophoretic skin testing more preferable than the intracutaneous technique.

Hill,[98] reporting on pollen sensitivity in children, found that in 100 asthmatic children, 84 per cent were positive to one or more pollens, and 90 per cent of these reactions had clinical significance. Hill stressed that in asthmatic children, pollen sensitivity is very common. In 100 consecutive cases of respiratory allergy, eighty were asthmatic, and twenty were hay-fever cases, with a high proportion of the children beginning with hay fever, and progressing to pollen asthma. The author stated that in children pollen sensitivity is not of the same degree as in adults, so that they frequently fail to give positive tests to scratch test materials, and that the intracutaneous test will frequently reveal positive tests which the scratch test has failed to reveal. Scratch tests are done as a rule, followed by intracutaneous tests, if the patient has seasonal symptoms with negative scratch tests. In twenty of thirty patients who failed to give positive skin tests by the scratch method, intracutaneous tests gave positive reactions to one or more pollens in fourteen patients. The author states that uncomplicated pollen allergy does not exist in the asthmatic pollen-sensitive child, but that multiple sensitivity is the rule, revealing sensitivities to other inhalant or environmental allergens. Hill[97] investigated food sensitivities in 100 asthmatic children, using twenty-seven food substances. In all, there were 218 positive reactions obtained. Twenty per cent proved clinically significant, 8 per cent had vomiting and hives, and in 72 per cent there were no connections at all.

In twenty-seven spinach skin-test-positive patients, only 2 per cent were able to be clinically correlated. In twenty-five fish skin-test-positive patients, fourteen were proven clinically significant. In twenty-two potato skin-test-positive patients, none were proven clinically significant. In twenty-one egg skin-test-positive patients, eleven were proven clinically significant.

Cohen and Abrams[43] recorded active allergy as a common cause of growth failure. Control of active allergy is accompanied by a corresponding growth repair, provided an adequate diet is present. The use of the Wetzel Grid offers a simple inexpensive and reliable method of detecting early growth failure.

London[116] described the development of a typical case of fall pollenosis in an eighty-three-year-old woman who lived in the same area for the past forty-seven years. Skin tests were positive to ragweed, dust, wheat, flaxseed and grass pollens. Her serum was also capable of giving a positive passive transfer.

Ralph Bowen[24] reports of his experience with hay fever "X" during the year of 1948. Hay fever "X" begins in early April and continues until mid-August in and around the Gulf Coast region. In 1948, the symptoms attributed to this condition were less in their patients, and certain factors associated with hay fever "X" decreased. The fig trees had less molds on them than usual, and the small white citrus fly, which come in through the ordinary screen in great abundance, was an infrequent visitor. These two factors have been investigated as etiological agents and have been proven negative in relation to hay fever "X."

Mitchell, Sivon and Mitchell[133] report the occurance of vulvo-vaginal pruritus associated with hay fever. This condition was noted in eight children between the ages of two to eleven who suffered from ragweed pollenosis. Hyposensitization therapy with ragweed pollen, or removal to a pollen-free environment, was effective in controlling the symptoms. Itching was most intense in the region of the mucocutaneous junction between the vulva and the vagina. The only visible skin changes were those resulting from scratches.

Shulman[163] studied the use of ragweed ointment in determining seasonal variations of ophthalmic sensitivity. This investigation included the study of variation of ophthalmic sensitivity to ragweed pollen before, during, and after treatment with ragweed extracts. Simulating nature, a preparation of whole ragweed pollen in a non-irritating ophthalmic ointment was prepared. One hundred patients were tested 591 times over a two-year period. Treated as well as untreated cases were included. A large percentage of the cases tested showed a rapid diminution of eye sensitivity, concomitant with a rising tolerance of pollen dosage.

Another group of patients showed an initial diminution of eye sensitivity, followed by a fixation of eye sensitivity at a moderately high level. In these cases, pollen dosage was not tolerated above the level of fixation of the ophthalmic sensitivity. A third group of patients showed positive ophthalmic reactions with high dilutions of pollen. Prolonged treatment caused no diminution of ophthalmic sensitivity. In these patients, pollen dosage was poorly tolerated.

Tuft and Blumstein,[177] in studying patients for maximal breathing capacity and breathing reserve, noted in four of twelve hay-fever patients that they showed signs of bronchial constriction.

Lowell and Schiller,[120] studying changes in vital capacity as means of detecting pulmonary action to inhaled aerosolized allergenic extracts in allergic individuals, showed that a reduction in vital capacity followed the inhalation of certain pollens and dust. In some instances, a fall in the vital capacity was observed in the absence of signs of subjective symptoms of asthma. With their limited experience, they indicate that this method may be helpful in diagnosis. The technique has the advantage that pulmonary reactions indistinguishable from spontaneous asthma may be produced and measured under controlled conditions. This method is also valuable in studying the effects of drugs on asthma-like responses.

Curry[50] compared the action of acetyl-beta-methyl choline and histamine on the respiratory tract in normals, in patients with hay fever, and in subjects with bronchial asthma. Mecholyl and histamine caused a slight reduction or increase in the vital capacity of the normal individual; however, in hay-fever patients there was a definite lowering in the vital capacity, especially during the pollen season. Criep,[46] in discussing practical aspects of allergic rhinitis, points out that in addition to the specific factors, the nasal membrane is also affected by climatic conditions, by irritating fumes and chemicals, by emotional factors, by endocrine factors, by the nasal obstructions and infections. He also points out that seasonal allergic rhinitis may be produced not only by pollens but also by spores of certain molds, by rusts and physical agents.

An interesting approach to the subject of vasomotor rhinitis and allergic rhinitis is discussed by McGrath[130] from the homeopathic point of view.

DRUGS

Cohen and VanBergen[45] reported their findings on the pharmacology and clinical experiences with Isuprel. In their hands, this drug has proven an effective agent in the control of the milder asthmatic symptoms.

The Council of Pharmacy and Chemistry[137] reported on Aleudrine sulfate through the activity of the Therapeutic Trials Committee. This compound was first tried clinically in Germany during the last war, and was found to have a profound bronchodilator action in laboratory animals, and unlike epinephrine and ephedrine, to have a vasodilator action. This action was thought so desirable as to warrant thorough investigation of its effects in asthma and other allergic conditions. Preliminary work indicates that it is not as potent an agent in man as is indicated by animal study. Furthermore, when given by intramuscular injection or by mouth in doses sufficient to exert a significant bronchodilator effect, patients may experience typical anginal attacks and show electrocardiographic changes compatable with

coronary constriction. There is some indication that these serious side effects can be mitigated by administering the drug sublingually and by inhalation.

The writers[105a] of this paper have had considerable experience with Aleudrine sulfate (isopropyl-epinephrine), known on the market as Isuprel. Our results corroborate that of the council's report exactly. We wrote that in no way can Isuprel take the place of epinephrine; however, the use of Isuprel sublinqually allows the patients greater ease in controlling minor asthmatic attacks, as well as the bronchospasms associated with coughing in the allergic. We found that the use of Isuprel by mouth or by intramuscular injection led to side reactions that precluded its use. The use of Isuprel by inhalation in the strength of 1:200 was in no way as profound as epinephrine 1:100; however, it is another drug in our armementorium, useful in bronchial asthma. This drug, in our opinion, will find its greatest use through the sublingual route, and secondly, by inhalation. It will definitely be accepted as one of the better sympathomimetic drugs, closely resembling epinephrine, having great bronchodilator effect and less of the pressor effects of epinephrine.

Krasno, Grossman and Ivy[109] investigated the use of "norisodrine" sulfate dust (Aleudrine) by inhalation. In their hands they found that the drug gave complete relief in twenty-four asthmatics. This drug was given in conjunction with some other suitable symptomatic drug. The authors found dizziness and/or palpitation in association with slight tachycardia and a fall of blood pressure in twenty-one of the twenty-four patients.

Herxheimer,[96] writing on the effect of Aleudrine in bronchospasm, says it is effective in relieving attacks of bronchospasm. The drug can be administered sublingually or inhaled. Tolerance to the drug is acquired by some patients. The optimal dosage varies widely in different people and should be determined in every case by spirometry.

Dunlop and Hunter,[38] in attempting to repeat Herxheimer's work, found that they could not agree with him because he did not control his experimental subjects. Herxheimer thinks that the negative results obtained by Dunlop were due to suboptimal doses.

In a note in the *JAMA*[106] the subject of "khellin" is discussed. They state, "That khellin may have further uses is suggested by the observation that after a single intramuscular injection of 200 to 300 mg., complete and prolonged relief was obtained in forty-one of forty-five patients with severe bronchial asthma; and even this fairly large dose had no effect upon the blood pressure. It has, moreover, relieved attacks resistant to adrenaline and aminophylline. Whether, as suggested, khellin is safer than aminophylline is not yet certain, for experience with it is so far small. If, however, khellin is to come into general use, preparations of it must be purified and standardized, for there is some evidence that the impurities in Ammivisnaga may be toxic."

Gilman,[78] in a very excellent article on the pharmacology of drugs used in allergic conditions, discusses them from the theoretical point of view. The theory of chemical mediation with particular reference to the action of acetylcholine and sympathin is outlined. The author points out that the term "antihistaminic" is a poor one since they do not by themselves cause any prominent degree of muscular relaxation or have any effect on the peripheral vasculature in their own right; also, that we are not dealing with physiologic antagonists but with a type of blocking agent. An interesting note by the author is the statement that "the administration of arsenic may in some way be related to the stimulation of the lymphoid and myeloid tissue in the production of antibodies, and may explain the alleged success of Fowler's solution in allergy."

Curry, Fuchs and Leard[51] report their observations, clinical and experimental, with

Orthoxine. Orthoxine (orthomethoxy-beta phenyl-n propyl-methylamine hydrochloride) is a new sympathomimetic compound, which, like ephedrine sulfate, is an active bronchodilator when given by mouth, but in contrast has relatively little pressor or central nervous system simulating effect. In view of the obvious advantages of such a compound in the treatment of bronchial asthma, the following studies were made: In fourteen asthmatic patients, asthma-like attacks with reduction in the vital capacity were induced by the parenteral injection of methacholine and histamine. Orthoxine in 200 mg. doses and ephedrine sulfate in 30 mg. doses were compared by their ability to protect against the reaction to histamine and methacholine according to techniques previously described. Another group of twenty-one-patients with bronchial asthma were given Orthoxine and ephedrine sulfate, and clinical response and side reactions were noted. In both groups of patients the effects of Orthoxine and ephedrine sulfate were comparable, but undesirable side reactions were not experienced after Orthoxine. In twenty-four subjects given 100 to 200 mg. of Orthoxine, only two showed a slight elevation in the blood pressure, and tachycardia was not observed in any case. It appears that Orthoxine has a definite place in the management of mild bronchial asthma, since it is an effective bronchodilator, is active when given by mouth, and has relatively little pressor or central nervous stimulating effect.

Wittich,[191] in his report of the "Clinical Evaluation of Orthoxine," said that "it is not affected by digestion, may be given orally, doesn't cause nervousness or central nervous system excitation." It is good for the prevention of reactions which follow the injection of pollen or inhalant extracts, and is best used with barbiturates. It is also useful with synthetic amines such as theophylline, and aminophylline. It is comparatively free of side effects. In 175 patients, the author reports seventy-three good results, sixty fair results, and forty-two poor results.

Simon[165] reports on the use of Nethaphyl. His patients preferred Nethaphyl with phenobarbital, to Amodrine, Tedral or ephedrine with Amytal. The author had good relief without side reactions of tachycardia, palpitation or rise in blood pressure, and nervousness. There were no toxic reactions sufficient for discontinuation of the drug.

SPECIFIC TREATMENT

Very little has been added to the specific treatment of pollenosis. Doyle[55] describes his method of desensitization by way of the nasal mucosa. However, he first uses injections by the intradermal route, and then continues by injecting the nasal mucous membrane, until a dose of 1 c.c. is reached. Local anesthesia of the mucous membrane, with 1 per cent Neo-Synephrine, 1 per cent Privine and 10 per cent Benadryl is used.

Loveless[117] has continued with her adjuvant treatment of hay fever, using emulsions of pollen extracts with fava alba and mineral oil in total doses of 1,000 to 2,000 units. She has been able to go from 1,000 to 7,000 units in two visits. The conjunctival tests, as well as passive transfer tests, are used to determine clinical response as well as the patients' improvement.

Jennes[102] of Connecticut, in a general discussion of the subject, calls attention to the specific therapy of secondary allergies during a hayfever period.

Henson[94] discusses specific treatment of pollenosis from the standpoint of Floridians.

Harley of England[90] discusses preseasonal, as well as coseasonal treatment of hay fever, and includes a discussion of the antihistaminics used in England.

Hansel[88] recommends the coseasonal method of treatment because it is safer, more economical, and gives satisfactory results. The control of non-pollen sensitivity is absolutely necessary in the management of the hay fever patient. In his

histamine five to ten minutes after physical exercise. The appearance of allergic manifestations after physical exercise in patients suffering from hay fever, together with a definite rise of blood histamine, seems to suggest that blood histamine has a significant role in allergic reactions produced by physical exercise.

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Walzer and Golan[183] evaluated the electrophoretic method of skin testing. The method was investigated with a special small type electrode, a current density of 0.5 milliamperes, a three-minute exposure and two drops of a 0.1 mg. nitrogen ex-

injections of vitamin B_2 (riboflavin), in 5 mg. doses, were quite effective during the acute stage of the disease, despite the fact that avitaminosis was not present; riboflavin by mouth in no way affected the course of the disease. No explanation for the mechanism of action of riboflavin in vernal catarrh was offered.

The use of 10 per cent argyrol nasal packs was decried in the answer of a query in the *JAMA*,[139] which stated that "the use of mild protein silver packs in allergy is certainly contraindicated. It will lead to chemical irritation of an already irritable, hypersensitive mucosa."

Montreymand[56] discussed the treatment of hay fever, and in addition to specific and nonspecific desensitization, he used antihistaminics as well as gelsemium.

ANTIHISTAMINICS

From perusal of the literature on the antihistaminics it is abundantly clear that enough care has not always been taken to eliminate from the clinical trials those factors which contribute to erroneous clinical impressions. It is likely that herein lies the explanation of the otherwise irreconcilable variation in apparent efficacy of these remedies in the hands of different workers.

Haley[83] presented an excellent review of the antihistaminic drugs in general, giving a summary of the principal actions of histamine, the chemistry of the antihistaminics, their general pharmacology, their action in blocking histamine and their clinical usage. In his summary he stated that the results obtained in asthma and in histamine-induced gastric secretion were disappointing, and indicate that the drugs are not true antihistaminics on the particular body system involved, or that some other agent causes the symptoms attributed to histamine. He felt that the toxic effects of all these drugs are similar, and excessive dosage was dangerous.

Marsh[126] reviewed the pharmacology of the antihistaminics and commented on their mechanism of action, namely, competitive inhibition. These agents do not prevent the allergic response in the body; they prevent only the resultant symptoms (that is, when they are effective at all.) With allergies to known causal agents, avoidance of contact, or gradual desensitization to the allergen, produces much less physiologic unbalance in the body, and much less hazard of undesirable effects. Although no symptoms indicative of chronic toxicity have been observed, he suggested that treatment be continued only eight weeks at a time.

Following are some comparative studies on various antihistaminic drugs.

Aaron and Criep[1] compared the action of Neohetramine and Thephorin. In this study, 243 patients were given Neohetramine and 382 were given Thephorin. They felt that both drugs had good antihistaminic and anti-anaphylactic properties and that they compared favorably with the other histamine antagonists in their clinical value in allergic states. In addition, they exhibited a relatively low incidence of side effects. Toxicity studies were performed on hospitalized patients who received 300 mg. of the two drugs daily, and no significant changes were discernible in the urine, blood pressure and electrocardiographs. However, in two cardiac patients who used Thephorin, the T wave became inverted but returned to normal on discontinuance of the drug. Their report indicated that of the patients who had hay fever and were given Neohetramine, 33 per cent obtained complete relief, 27 per cent moderate relief, 22 per cent slight relief and 18 per cent no relief. The figures on Thephorin were as follows: 44 per cent obtained complete relief, 32 per cent moderate, 14 per cent slight and 10 per cent no change whatsoever. The incidence of side effects was 10 per cent with Neohetramine and 23 per cent with Thephorin.

Kleckner[108] gave a clinical appraisal of three drugs: Benadryl, Pyribenzamine and Anthallan. He felt that Benadryl was the most potent drug of the three in the treatment of seasonal allergic rhinitis. Pyribenzamine, on the other hand, had the

advantage of causing less than one-half the toxic side reactions of Benadryl; he felt that some of the serious side reactions can be quite hazardous. He stated that Anthallan was effective in the treatment of allergic rhinitis, but its outstanding quality was that it elicited no toxic side effects. It was his opinion however, that these drugs were no substitute for an adequate allergic investigation and that their indiscriminate use was to be thoroughly discouraged.

McGavick et al,[128] comparing the toxic manifestations produced by Benadryl and Pyribenzamine, felt that Benadryl produced a preponderance of sensorial disturbances while Pyribenzamine produced mainly gastrointestinal manifestations, and that the incidence of reactions were about equal for the two drugs.

Gay, Landau et al[77] presented their clinical observations on various antihistaminic drugs used on 428 cases of seasonal and perennial allergic rhinitis. The dosage employed was 50 mg. every four to six hours for all the drugs except Antistine, in which case 100 mg. was used, and Hydryllin, where 25 mg. was used. The drugs studied were Pyribenzamine, Hydryllin, Antistine, Neo-Antergan, 1913 (Searle), 1721 (Searle), Histadyl, and Chlorothen. In general, 60 to 76 per cent of the patients were benefited, best results being obtained with Pyribenzamine, Hydryllin, Antistine and Neo-Antergan. Changing from one drug to another produced results equal to, worse than, or better than the original drug. There was no rule as far as one drug being more or less effective than another; this varied from patient to patient. Side effects varied from 13 per cent with Antistine to 42 per cent with 1913 (Searle). Their conclusions from this study were that no parallelism existed between effectiveness against histamine in guinea pigs and effectiveness against human allergy. The wide differences observed in potency with histamine experiments were not found clinically. They felt that it is fortunate that we are able to choose among several preparations and to change from one to another when necessary, but that these drugs cannot replace the diligent search for the etiological factor and its elimination if found.

Arbesman[13] conducted some comparative studies using Pyribenzamine, Hydryllin, Neo-Antergan, Antistine and Neohetramine and reported the following results in extrinsic allergic rhinitis. Eighty per cent were improved on Pyribenzamine with an incidence of side effects of 26 per cent. With Neo-Antergan 63 per cent were improved and side effects occurred in 33 per cent. For Hydryllin the figures were 56 per cent and 35 per cent, for Neohetramine 43 per cent and 16 per cent, and for Antistine 30 per cent and 14 per cent. All of the patients did not use all the drugs, but from the data obtained, Pyribenzamine offered more relief than any of the others. Although Neohetramine and Antistine appeared "less potent," they proved to be the most effective drugs in certain patients, and the incidence of side effects was least with these two drugs, and they could often be tolerated when Pyribenzamine and the others had to be discontinued.

Weiss and Howard[186] compared the effectiveness of Neo-Antergan and Pyribenzamine with other forms of therapy of seasonal allergic rhinitis. They divided their hay-fever patients into six groups. One group received hyposensitization treatments plus placebo, the second and third group received hyposensitization plus one or the other antihistaminic as needed. A fourth and fifth group received placebo injection plus an antihistaminic, and the sixth group was given placebo injections plus placebo tablets. From their figures it would appear that hyposensitization treatment alone was just as effective as such therapy supplemented by Pyribenzamine or Neo-Antergan. However, they felt that this was not exactly true, as when they evaluated their results according to the type of hyposensitization treatment employed, they found that a preponderance of the patients on Pyribenzamine and injection therapy were given coseasonal treatment, which they consider the least effective form. Neo-Antergan was found to produce more side reactions and have slightly less effect in supplementing injection therapy than Pyribenzamine. The anti-

histaminic drugs do not prevent the development of seasonal asthma. They finally concluded that hyposensitization therapy supplemented by antihistaminic medication is the treatment of choice for hay fever.

Waldbott and Young[182] studied the effect of six antihistaminics, namely: Antistine, Neo-Antergan, Neohetramine, 3277 R.P., Trimeton and Benadryl. The drugs were administered only when symptoms were in evidence. They stated that in general it was apparent that the drugs closely resembled one another in the degree and duration of relief afforded; the beneficial effect, when obtained, persisted from four to six hours. However, the action of 3277 R.P. appeared to be decidedly more protracted. They concluded that no decided difference in the efficacy of each individual drug was noted except that the effect of 3277 R.P. appeared to be more protracted than that of the others; the usual side effects occurred and were most pronounced with this drug. However, it would seem to us that the actual figures presented on efficacy belie such conclusions; to use two examples, namely, 62 per cent received marked relief when using Trimeton, and only 28 per cent received the same degree of relief with Neo-Antergan.

Spain and Pflum[167] evaluated the use of various antihistaminic drugs in 2,500 hay-fever cases. They felt that 60 to 75 per cent showed improvement, the greatest improvement occurring in those patients with slight or average pollen sensitiveness who were also undergoing hyposensitization. Relief when it came, was usually within a half hour; patients with high degree of sensitivity obtained disappointing results. They felt that there was no prolonged protection and that unpleasant side effects prevented extended treatment when necessary. It was their opinion that this class of drugs should not be used to control constitutional reactions. These drugs are palliative, being in no sense curative, and developing no specific immunity for the patient. In emergencies they are not effective enough to replace epinephrine; even in moderate allergic attacks they are often less satisfactory than epinephrine or ephedrine. Unpleasant side effects occurred in approximately one-third of all cases. There is great variation in individual effect and dosage necessary to produce the effect; these drugs should not be used without supervision. In general, they concluded that the antihistaminics have proven to be most helpful agents against those allergies whose symptoms result from sudden and acute edema, and against many forms of pruritus. They are not intended to replace specific immunizing procedures except possibly in the mildest cases.

A very interesting study was conducted by Holtkamp et al,[99] comparing Benadryl, Pyribenzamine and Hydryllin on the basis of their effect in therapeutic doses on mental ability, reaction time, two-point discrimination distance, pulse rate, blood pressure and respiratory rate. In over one-half of the subjects tested, mental ability, reaction time and minimum distance of two-point discrimination was appreciably altered by these drugs. Pyribenzamine showed a decrease in efficiency in a greater number of individuals than did Benadryl, but the latter occasionally caused decreases of considerably greater magnitude. Hydryllin caused an increased efficiency in a majority of the subjects but adversely affected a few. It would have been highly desirable to have had a larger series of cases upon which these interesting studies were performed.

Serafini,[160] using various histamine antagonists, found that they could modify the histamine tolerance curve in allergic patients. Using Antergan in fifteen hay-fever patients, he found that two-thirds of the cases received complete relief and the other one-third were afforded partial relief. This relief was temporary and palliative; side reactions occurred in two cases. It was interesting to note that constitutional reactions in the course of routine hyposensitization therapy disappeared when the drug was given. He felt that his experiments afforded further evidence that histamine plays an important, although not exclusive role in allergic conditions in human beings.

Halpern and Hamburger[85] continued their research on synthetic antihistaminics, reporting this time on Phenergan (3277 R.P.). They administered this drug orally in dosages of 25 to 100 mg. daily (in some cases as high as 200 mg.). Its use in 142 hay-fever patients resulted in complete disappearance of all signs and symptoms in ninety-eight (69 per cent) of them. Partial relief, consisting of cessation of sneezing but not affecting nasal congestion, occurred in thirty-six cases. The eight remaining cases were unaffected, but these patients could not tolerate therapeutic dosages. In the majority of the cases, 25 mg. daily suppressed sneezing, but from four to six times this dose was necessary to give complete relief of all symptoms. Twenty-five per cent of these patients exhibited slight degrees of drowsiness with vertigo and irritability—usually neutralized by Benzedrine; these symptoms usually disappeared when treatment was continued. They felt that the experimental and clinical results indicated that Phenergan was a powerful antiallergic drug. This drug, interestingly enough, influenced several conditions in which no allergic cause could be demonstrated, such as pulmonary edema due to epinephrine or poison gas and orthostatic albuminuria. In consequence, the problem of the mechanism of action of Phenergan still has to be elucidated; their experimental work suggests that this compound acts on capillary permeability. Halpern[84] found that injection of this drug greatly increased capillary resistance in eight of ten patients with allergic conditions, while on the other hand no such result was obtained in nonallergics. It is very striking to note that most of the pathological conditions controlled by Phenergan are characterized by serous extravasation through the capillary wall.

Another of the newer antihistaminics reported upon, was Trimeton. Wittich[190] used this drug on thirty-three hay-fever patients, twenty-five of whom received good results, six fair and two none. The total improved in the pollenosis group was 90 per cent with no side reactions. The most beneficial effects were obtained when used in conjunction with immunization measures and for preventing systemic reactions with high dosage of pollen extracts by administering a 25 mg. tablet about one-half hour before injections.

Ethan Allan Brown[27] used this same drug in 227 patients, of whom 61 per cent became completely symptom-free and 22 per cent received moderate relief. Of those having hay fever, 90 per cent were relieved. Side reactions consisted chiefly of drowsiness in 16 per cent of the patients; 6 per cent had to discontinue the drug because of side effects.

Another new drug that received considerable attention was Decapryn. Brown and Werner,[25] reporting on its pharmacology, demonstrated by laboratory experiments a comparatively low toxicity and potent antagonistic action to the effects of histamine on various tissues. A high degree of antagonistic action follows its use by all routes of administration; cutaneous effects of histamine, as measured by whealing reaction in rabbits, were antagonized. It has considerable local anesthetic activity. These same authors[26] also reported that this preparation protected experimental animals against both natural and acquired hypersensitiveness and anaphylaxis.

E. A. Brown, et al[28] studied the effects of this drug on 140 consecutive patients, seventy-one of whom were private cases and sixty-nine clinic cases. The dosage used varied from 6.25 mg. to 150 mg. four times daily, the average being 12.5 to 25 mg. Of the private patients with hay fever, fourteen derived excellent relief, three moderate relief, with slight side effects in one patient. Six patients with asthma and hay fever were relieved of nasal symptoms with no effect on their asthma. In twenty-six clinic patients with hay fever, eighteen obtained excellent relief, six moderate, and two negligible relief. Slight side reactions occurred in three patients, moderate ones in six, and severe in only one. In six patients who had both asthma and nasal symptoms, excellent results were obtained in both nasal and bronchial symptoms in two, excellent as to nasal symptoms alone in one, moderate relief of nasal symptoms in two, and of asthmatic symptoms in one, and negligible results in

another one. Drowsiness of a moderate degree was reported by one, and severe drowsiness by another. In general, 80 per cent of their patients with typical hay-fever symptoms were relieved by Decapryn. Drowsiness was the most commonly encountered side reaction, and was observed in about one patient out of six. The most disturbing side effects were apparent in those taking comparatively high doses. In the 12.5 to 25 mg. dosage range they felt that fewer than 10 per cent occurred. Of those who had previously taken other antihistaminic agents (fifteen had taken Benadryl, seventeen Pyribenzamine and sixteen had had both drugs) one preferred Benadryl, three Pyribenzamine and of the remainder, all but one, who was relieved by none, preferred Decapryn.

Feinberg and Bernstein[68] studied the effects of Decapryn on eighty-one patients with seasonal hay fever due to grasses, ragweed pollens or fungus spores. Some of these patients were untreated while the majority had received previous desensitizing injections. Satisfactory relief was obtained in 62 or 76 per cent of their patients; this relief was temporary. The patients in their series felt that there was a tendency to longer duration with this drug than with other antihistaminics. The dose varied from 12.5 to 50 mg. They found that in some patients a highly soporific effect was obtained with this drug, and therefore large doses should not be prescribed without previous trial on smaller doses. The incidence of side effects encountered was 34 per cent of their total patients, with sedation and sleepiness being the most prominent effects. After six months' trial, no serious or remote toxic effects were manifest. They made note of an important fact reported on by other investigators as well, namely, that in patients with hay-fever asthma, the antihistaminic may relieve the hay fever but *not* the asthma; desensitization is highly effective in the prevention of this type of asthma, and it is obvious that the antihistaminics should not be depended upon in such cases.

Sheldon et al[162] reported on the use of Decapryn by fifty-five patients with hay fever. They subdivided the symptoms exhibited by these cases, giving the results obtained individually. They classified results as satisfactory if there was over 50 per cent relief, and unsatisfactory if relief was less than 50 per cent. Sneezing occurred in forty-one patients, thirty-one of whom obtained satisfactory relief. Rhinorrhea occurred in fifty-four patients, with satisfactory relief being obtained in forty-three. Of thirty-seven who complained of nasal obstruction, twenty-six claimed satisfactory relief. Thirty-one had itching and twenty-seven were relieved; thirteen complained of fatigue, with satisfactory results in eight patients. In 57.2 per cent of these patients, side reactions of drowsiness occurred. The duration of the physiological effect was from four to twenty-four hours after a single dose, and they found no evidence of chronic toxic manifestations. They felt that the beneficial effects from Decapryn would appear to be of a similar magnitude to those reported for Benadryl and Pyribenzamine, but of longer duration.

An antihistaminic, Thephorin, with a radically different chemical structure from that of previous histamine antagonists, received considerable attention. Sternberg and Gottesman[170] used this drug in forty-one hay-fever patients. Eighteen of these had good results, four had fair, and nineteen had no results. All of the subjects were given hyposensitization therapy but were not adequately relieved. They used the drug on a total of seventy-six patients with various allergies, and found side effects in only five of them, all of whom complained of insomnia. They felt that Thephorin is an effective antagonist. They stated that it must not be forgotten, though, that all antihistaminic agents are only palliatives, and none of these preparations will relieve the physician from attempts to recognize the offending allergens, and to eliminate them, or to hyposensitize the patient.

We had a not inconsiderable experience with this drug during its trial stage and feel that this preparation is a useful addition to our armamentarium, especially be-

cause of its stimulating side effects when they do occur, and secondly, for the fact that the incidence of any side effects is usually small.

Frank[74] reported on its use in 140 patients, thirty-seven of whom had hay fever, and thirty-one of these benefited from therapy. Speculum examination proved objectively the shrinking of the congested nasal mucosa, sometimes within one-half hour after the initial dose. As much as 400 mg. daily was tolerated without untoward effects. In general, symptoms were controlled by daily dosage of 50 to 150 mg. Side effects occurred in 38.6 per cent, being severe in 12.8 per cent. Insomnia was the most commonly encountered symptom; excitability was another. In general, the majority of side effects were manifestations of central nervous system stimulation. Reactions were less common in children than in adults.

Criep and Aaron[47] had 180 patients with seasonal hay fever using Thephorin, with 44 per cent reporting complete relief, 32 per cent moderate relief, 14 per cent slight relief and 10 per cent no relief. Many of these patients were receiving concomitant injection therapy. Of the total of 389 patients with various allergic manifestations, that were used in their study, 23 per cent had side reactions. The majority of these were of a stimulant nature or those referable to the gastrointestinal tract. They concluded that this drug was an effective antihistaminic agent both experimentally and clinically. Toxicity studies did not reveal anything of note, and they felt that clinically Thephorin was of as much value as the other antihistaminics in the treatment of allergic states.

A very interesting study was conducted by Boyd et al.[23] Thephorin was given orally to 100 selected nonallergic subjects in daily doses varying from 75 to 700 mg. for periods of one week or more. These patients recorded all symptoms of any nature not present prior to administration of the drug. The most frequently observed unpleasant manifestation of the action of this drug was dryness of the mouth, which occurred in 22 per cent of these patients, being most marked at higher dosage levels. In smaller doses, 300 mg. daily or less, insomnia was the most common manifestation. In all, forty-two of the 100 subjects developed one or more toxic symptoms while taking Thephorin. The use of this drug in the above dosage range for four or more weeks was not associated with any significant changes in electrocardiograms, nonprotein nitrogen, blood count or urine studies. When compared with other drugs that have antihistaminic activity, namely, Benadryl and Pyribenzamine, Thephorin is less toxic weight for weight in daily doses ranging from 150 to 600 mg.

Cohen, Davis and Mowry[41] reported that 105 patients out of 161 who had allergic rhinitis obtained good results using Thephorin; twenty-three had fair; and thirty-three poor results. Of a total of 292 patients who took the drug, fifty-four had side reactions, thirty-three of whom complained of nervousness. Peters[136] described his clinical experiences with Thephorin in 142 cases, sixty-eight having hay fever and thirty-four having both asthma and hay fever. He felt this preparation was effective in 97 per cent of the hay-fever cases. In those patients having both asthma and hay fever it was effective in controlling the symptoms in 91 per cent. This is truly a remarkable record, especially in view of the fact that it is generally accepted that the antihistaminics are ineffective in preventing asthma in those cases of pollenosis of the hay-fever and asthma type. Total side effects reported in the entire group of cases were 11 per cent, and in only five cases were symptoms severe enough to necessitate discontinuance of the drug. The types of side reactions most commonly encountered were insomnia and gastric disturbances.

Lehman[113] reported on his laboratory experiments with Thephorin and felt it to be a potent antihistaminic on isolated guinea pig ileum, in the spray test, against intracardial histamine and against anaphylactic shock; it was also a potent local anesthetic.

Vanderbrook and Olson et al[178] did numerous pharmacologic experiments with Pyrrolazote, another histamine antagonist, and demonstrated it to be a potent antag-

onist to many of the pharmacologic responses of histamine. When compared with Pyribenzamine, it was effective for a longer period and had similar antianaphylactic properties. It appeared to be from one half to one twentieth as toxic as the latter drug. Chronic toxicity studies in rats indicated that it was not harmful.

One hundred and sixty-five patients with seasonal and perennial allergic rhinitis were treated by Waldbott[181] with Neohetramine; 68 per cent were benefited; a little over 10 per cent had side effects, with dizziness and drowsiness being most prominent. He felt that, in general, the results compared favorably with corresponding observations on other antihistaminic drugs.

Bernstein and Feinberg,[18] using the same preparation, reported that 48 per cent of sixty-five patients given 50 mg. doses obtained satisfactory relief, and in thirty patients given 100 mg. doses 70 per cent were satisfactorily relieved. As compared to some of the other antihistaminic compounds, larger doses seemed to be required for therapeutic effect. They felt that with doses producing a reasonable degree and incidence of therapeutic effectiveness, the incidence and degree of side reactions were less than with most other antihistaminic drugs. They felt this drug to be a useful addition because of its apparent low toxicity.

Scudi and Reinhard,[158] commenting on this aspect, found the drug to be about one half as toxic as other antihistamine agents from intraperitoneal toxicity studies in mice.

Criep and Aaron[48] employed Neohetramine in 50 mg. doses every four hours, as necessary, in 124 cases of hay fever; 33 per cent obtained complete relief, 27 per cent moderate, 22 per cent slight, and 18 per cent no relief. Relief when obtained lasted three to six hours. Many of these patients were receiving concomitant hyposensitization therapy, and evaluation was by comparison with periods when the drug was not taken. Side reactions occurred in 10 per cent of their cases; nervousness and palpitation seemed to occur most frequently. They felt that this drug was as effective as the other histamine antagonists, both experimentally and clinically. Toxicity studies on seventeen patients failed to reveal any changes of note.

Alperstein[11] reported on the use of two halogenized ethylenediamine derivatives (Bromothen and Chlorothen) supposedly less toxic and more effective than Pyribenzamine. He used these drugs on twenty-six patients who had experienced side effects from Benadryl and Pyribenzamine and had had to discontinue their use; these were cases of allergic rhinitis and hives. Eighteen of these patients received Chlorothen and eight Bromothen; all of these patients manifested relief in fifteen to thirty minutes with a 50 mg. tablet, and none experienced any side effects. Twenty-five additional patients with various allergic manifestations were given Chlorothen and twenty-two Bromothen; they all obtained relief and none experienced side effects. This was a preliminary report with no protocols and no conclusions except that further investigation was warranted.

We[61a] have had considerable experience with Chlorothen, upon which we reported at the recent meeting of the American College of Allergists, and unfortunately our experiences would not bear out the above glowing report.

The effect of a chemical combination of aminophylline with diphenhydramine—Hydryllin—was reviewed by Brown and Brown.[29] Of eighty-one patients with hay fever, thirty-nine obtained 100 per cent relief, twelve had 75 per cent relief, sixteen had up to 50 per cent relief and fourteen received no beneficial effects. Side reactions, of which drowsiness and dizziness were the most common, occurred in 35 per cent of the patients; because of the severity of these, twenty-one patients had to discontinue its use. However, it was their impression that side effects were notably less with this drug than with diphenhydramine alone. They seemed to get striking relief in pollen asthma. Markow,[125] using the same drug in twenty-seven

patients with hay fever, found that it was beneficial in fourteen of them (52 per cent). Toxic reactions occurred in 37 per cent of his patients, a third of which were severe enough to necessitate discontinuance of the drug.

Levin et al[114] used Antistine and Neo-Antergan in the treatment of hay fever and felt that these drugs were of value in this condition. It was their feeling that Neo-Antergan seemed to have more antihistamine properties, but at the same time gave more toxic reactions than Antistine. The results from the use of the drugs above were not as good as could be obtained with the combination of the drug and pollen hyposensitization. There was, however, only a little better result from the use of the drugs and hyposensitization than from the use of pollen hyposensitization alone. Apparently they felt that hyposensitization was still the method of choice, and the antihistaminic drugs cannot be considered as substitutes. Nonetheless these drugs are of value as adjuvants, in that they help to relieve some of the more severe symptoms, and shorten their duration even if only temporarily. We must never lose sight of the fact that a considerable number of toxic reactions occur, and they felt that, if used judiciously together with orthodox measures, antihistaminics were a valuable addition to our methods of treatment. In general, Antistine afforded relief in about 65 per cent of their patients with hay fever, and Neo-Antergan in about 70 per cent of the cases. Toxic reactions occurred in 36 per cent of the patients on Neo-Antergan and in 21 per cent of those using Antistine.

Southwell[166] used Neo-Antergan in fifteen patients with hay fever due to grass or grass and tree pollens. They were graded numerically according to the severity of their symptoms: grade 4, severe; grade 3, moderate; grade 2, slight, and grade 1, no symptoms. He used placebos interchangeably with the drug itself, the dose of the drug being 3 tablets (.1 gm.) three times daily. The severity of the hay fever symptoms while taking the drug was a figure of 1.5, whereas while on placebo medication the figure was 3.7. His impressions were, that the hay-fever symptoms were partially or completely controlled by Neo-Antergan and that the patients were unanimous in their praise of the preparation, and felt that they got better relief only from the most successful desensitization course. Side effects occurred in over 50 per cent of the cases; most of these were mild.

Calder[35] used Neo-Antergan in six hay-fever patients, with complete cessation of attacks in five, and slight symptoms only in the other one.

The dosage employed was 0.2 gm. three times daily until the end of the pollen season. He was of the opinion that this drug was an effective antihistaminic, but like all of these preparations it does not cure and must be given for as long as an effect is desired. When treatment is stopped, there is a quick relapse of the patient's condition. It was his feeling that desensitization remains the treatment of choice, and the antihistamine drugs should be used only where the offending antigen cannot be found, or pending desensitization. In this total series of cases (including thirty-eight with vasomotor rhinitis), mild side effects occurred in four. It is well to remember that clinical evaluation can be difficult since allergic manifestations are frequently self-limiting, and in chronic conditions spontaneous improvement may take place at any time, because of the sudden disappearance of certain inhaled or injected antigens or by spontaneous desensitization.

Winter et al[188] performed some chronic toxicity studies with Neo-Antergan in animals; the drug was administered to various animals for varying lengths of time up to six months. No toxic signs or abnormalities were found in these animals with the dose employed. They concluded that there was no evidence that this drug had any cumulative effect at small and moderate doses.

In two cases of tree pollen allergy, Hughes[101] used Antistine with complete control of symptoms in both. Each had notable conjunctival symptoms and both were satisfactorily relieved by Antistine-Privine eye drops. He also used the drug in several cases of preseasonal ragweed and grass hyposensitization therapy for the

prevention and control of reactions, and it appeared to be of value in allowing more freedom from reaction. His incidence of side reactions in treating forty-eight patients with various allergic complaints was 12.5 per cent.

Kaplan and Ehrlich[104] found that Antistine afforded some measure of relief in a majority of hay-fever patients to whom it was given. Such results were less evident, but still present, in many with perennial allergic rhinitis. The drug was very efficacious in children, because adequate dosage could be given with minimal side effects.

Friedlander and Friedlander[75] felt that Antistine produced some degree of symptomatic relief in 59 per cent of patients with allergic rhinitis. The effect on rhinorrhea and sneezing appeared to be greater than on nasal blockage. In those patients who had also used Pyribenzamine, a comparison between the two in the same patients indicated a greater effect on the part of Pyribenzamine in most instances, while a smaller percentage found Antistine superior. Side effects from Antistine were generally less frequent than with Pyribenzamine. In many instances those unable to tolerate Pyribenzamine could take Antistine in effective doses without side effects.

Linadryl, used by McGavack[128] in fifty hay-fever patients in a dosage range of 150 to 400 mg. daily, resulted in complete relief in twelve patients, some improvement in eight more, and no relief in thirty (60 per cent) of the patients. Of a total of 250 patients with all types of allergic manifestations, side effects were manifested in a little over 17 per cent. None became apparent until 250 mg. or more of the drug was taken daily; a tolerance frequently developed as the drug was continued. By far, the commonest complaint was drowsiness. They concluded that Linadryl has an action similar in nature to that of Benadryl but is probably less than one-half as effective, weight for weight; and if the dose were pushed to a point of comparable effectiveness in every case, it would probably cause an equally high number of unpleasant symptoms.

Intravenous Benadryl was given by Mackmull[123] to fifty patients in doses of 50 to 300 mg., and various systemic reactions were encountered, but none of sufficient severity to require treatment. Average systolic and diastolic blood pressures were elevated with large dosages. He felt that such intravenous doses of Benadryl were contraindicated in the presence of hypertension. Electrocardiographic changes of sufficient significance occurred after 200 to 300 mg. doses. The results of the experimental work of Chen et al[38] indicate that the joint antihistaminic effect of Adrenalin and Benadryl is additive, while the joint lethal toxicity of the two at low dosages of Benadryl Hydrochloride is synergistic in nature.

Preliminary studies conducted by investigators of NMRI[40] suggest that the toxic effects of Benadryl are such that piloting of aircraft during the course of the drug's action may be hazardous. In Queries and Minor Notes,[141] the question of the use of Benadryl and Pyribenzamine during pregnancy was asked. The query stated that the patient in question had taken these drugs during a previous ragweed season while pregnant and had aborted. The answer given was that, thus far, reports had not indicated that these drugs produced abortion. They further stated that if drug sensitivity existed, drug sickness might ensue which might have some undesirable effect in pregnancy.

Tomlinson[176] writes that at the end of the hay-fever season he saw two similar cases that he felt suggested a possible changed allergic state. Both patients were females who were given Benadryl (150 mg. daily) for their hay-fever symptoms, with complete suppression of these symptoms. After taking the drug for the season, they both presented an eczematous eruption of the face, neck and forearms, and with local therapy the eruption subsided. It occurred to him that the suppressive action of Benadryl may have transferred the reactions from the nasal mucous membranes to the skin. It would seem to us that aside from the theoretical implications involved,

certain other explanations would need to be invoked; for example, evidence that this may or may not have been a toxic side reaction.

Sachs[153] reported a patient who used 600 mg. of Benadryl daily and developed many untoward symptoms including hallucinations and jerky rapid speech. He then presented an excellent review of the literature on the subject of side reactions with the use of this drug, reporting such reactions in 46.4 per cent of 1210 patients. Drowsiness was the most frequently encountered toxic reaction. When the mode of administration is by vein, toxic reactions are more frequent, occurring in 65 per cent of forty-three patients; these reactions were more acute in onset, more severe and of shorter duration. Weakness was seen much more frequently when the drug was given intravenously. The untoward reactions that occurred were classified as (1) neuropsychiatric, (2) alimentary, (3) cardiovascular, (4) respiratory, (5) genito-urinary, (6) muscular, (7) ocular, (8) miscellaneous (pruritus, aggravation of allergic symptoms). The mechanism of toxic reactions has not been adequately explained except in those cases of sensitivity to acetylsalicylic acid (both drugs having a coal tar radical). These toxic side reactions are most common with higher doses; however, profound reactions have occurred following a single dose, and 600 mg. daily have been given without any. Toxic reactions occur on some occasions in the same patient on the same dosage while not at other times. It is not possible to correlate the dose level with the type of reactions. The occurrence of toxic effects may be minimized by reducing the dose, taking the drug after meals, using the initial dose in the evening, and prescribing stimulants. A large number of patients developed tolerance, and the side effects disappeared. Within several hours after discontinuance of the drug, in those cases of toxic effects, the manifestations usually disappear, and there is no evidence of any cumulative toxic effect.

Starr and Rankin[168] noted a child of eighteen months of age who had taken three to five 50 mg. capsules of Benadryl and developed convulsions, cyanosis and bulging eyes within a half hour. Upon admission to the hospital the child was comatose, threshing wildly about, with marked erythema of the face and extremities, dilated pupils that did not react to light, bilateral nystagmus and frequent toxic convulsions. He was treated by gavage with instillation of 6 c.c. of magnesium sulfate solution, 10 c.c. of phenobarbital and 75 mg. of Sodium Amytal intravenously. Gradual improvement took place in twenty-four hours. It might be interesting to note at this point, that with lethal doses in animals, death is preceded by excitement and convulsions. Blackman et al[20] reported a case of exacerbation of acute bronchial asthma following Benadryl therapy, terminating in a fatal outcome. The authors admit however, that the case in question cannot categorically be considered as due directly or entirely to Benadryl. The primary cause of death appeared to be severe central nervous system depression.

Brown[31] made a controlled study of side reactions to Pyribenzamine on patients who were receiving injections of typhoid vaccine. Forty-eight patients were given five 50 mg. tablets in twenty-four hours (some patients were used two to three times so that the total was 100 times). On fifty-six occasions, the dose of Pyribenzamine was doubled in thirty-seven patients. Nervousness, dryness of the mouth and headache were more frequent in the control group as compared to the 50 mg. Pyribenzamine group. Drowsiness, nausea, dizziness and insomnia were less frequent, but nonetheless quite evident, in the control group. All of the above side reactions were more frequent when the dose of Pyribenzamine was doubled. These data indicate that the 50 mg. dose of Pyribenzamine, which is the most frequently used dose, has a negligible effect in producing the stated symptoms, all of which have been ascribed to Pyribenzamine medication. These data indicate the importance of using controlled studies in evaluating the side reactions as well as the therapeutic effects of a new drug.

Fanburg[61] described a case of fever, secondary to Pyribenzamine medication.

Following discontinuance of this drug, the patient's temperature returned to normal. Subsequently this drug was readministered, with an abrupt onset of pyrexia, followed by an abrupt termination on discontinuance of the medication; this would seem to indicate that the drug was responsible for the fever.

The mode of action of antihistaminic agents was studied on atropinized guinea pig ileum by Alonso et al,[10] and their results indicated that the law of mass action was obeyed over a thousand-fold concentration range of both histamine and antagonist. The drugs studied were Benadryl, Pyribenzamine, Neo-Antergan and Chlorothen. They concluded that these results were in agreement with the theory that histamine and the above antagonists compete for the same cellular receptors. Rense[146] compared the action of histamine and antagonists on isolated organs in various ways as to their power to antagonize histamine, and his results showed that Neo-Antergan was first, 3277 R.P. second, Benadryl third, Antistine fourth, and Nupercaine last. He was of the opinion that of the five drugs employed in these studies, Neo-Antergan was the most specific; also that the activity of these drugs as local anesthetics appeared to be more nearly related to their activity against acetylcholine than to their activity against histamine.

Comparative studies of antihistaminic substances were made by Landau and Gay[111] by means of Dale tests, and they found three groups of potencies. The most highly potent were Neo-Antergan, Pyribenzamine, Chlorothen, Promothen and Histadyl. Of moderate potency were Benadryl, 1721 (Searle), and 3277 R.P., with Antistine being in the weakest group. However, one must not lose sight of the fact that it is well known that laboratory experiments of this type are not directly transposable clinically.

Winter[189] conducted experiments with guinea pigs and mice, using several antihistaminics together with barbiturates. Pyribenzamine, Benadryl, Neo-Antergan and 3277 R.P. were the preparations employed. He found that the potentiating effect of Benadryl upon the sedative action of these barbiturates was much greater than that of Neo-Antergan or Pyribenzamine. However, all the drugs employed prolonged the sleep-producing effects of barbiturates. These results appear to correlate with the reported incidence of sedation as a side effect in patients receiving antihistamine drugs.

Stavraky,[169] using ferrous sulfate by mouth in daily doses of 20 to 45 grains in conjunction with Pyribenzamine or Antistine, felt that the combination was most effective in alleviating allergic manifestations in eight patients with ragweed hay fever and asthma. Iron also seemed to relieve lassitude and drowsiness induced by antihistamine agents, making possible increases in doses of Pyribenzamine and Antistine with further benefit to the patient. As a precautionary measure, the iron was given with calcium to decrease the toxicity of the former substance. This highly interesting study would be more informative with a larger, more well-controlled series of patients.

After several years of trial with the various antihistaminic agents, it would seem apparent that most men would subscribe to the following conclusions: It must not be forgotten that all antihistaminic drugs are only palliatives. None of these preparations will relieve the physician from attempts to recognize the offending allergens and to eliminate them if possible, or to hyposensitize the patients to them. These drugs have a place *in conjunction* with the orthodox therapy when the latter does not adequately control the symptoms, or before that therapy brings relief to the patient.

MISCELLANEOUS

Rockwell[149] described eighteen synthesized derivatives of histamine and treated two cases of hay fever with no results. He pointed out that the therapeutic results of histamine therapy, when they are obtained, may be due to its pharmacological

action *per se* and not to the induction of any increased tolerance to histamine; he also noted that such preparation may be effective orally. Krueger[110] treated forty-one cases of allergic rhinitis with histamine acid phosphate on an ambulatory basis, and concluded that, in general, the results were poor, with twenty-seven failures, eleven cases improved, and only three with good results. A query in *JAMA*[143] was put as to whether any contraindication existed to the use of Hapamine and one of the antihistamine drugs. The answer was that if antibodies were produced (which is debatable) as a result of histamine-azo protein injections, the use of antihistaminics would not prevent their development.

This, of course, is also applicable to specific hyposensitization; in fact, as reported last year, there is a possibility of a greater production, since it may allow the use of larger doses of the allergen in question.

In an editorial appearing in the ANNALS OF ALLERGY,[60] the possible dangers arising from constitutional reactions, occurring following a shocking dose of pollen extracts, are discussed. Castburg and Schwartz reported important changes in the electrocardiogram. In each case, changes typical of anoxemia of the myocardium were noted.

Seltzer[159] noted convulsions following an injection of epinephrine in a twenty-six-year-old white man with asthma and rhinitis. The seizures lasted about thirty minutes and were of a general tonic and clonic type. Following injection of five minums of Adrenalin, the rate and depth of respiration increased until there was marked hyperventilation, which was followed by a convulsive seizure. It appeared that the convulsions were associated with a form of hyperventilation and tetany.

J. H. Black,[19] in a discussion of the effect of respiratory allergy upon the life and health of individuals, stated that pollen hay fever is of little significance so far as life expectancy is concerned. Asthma is a frequent sequel of hay fever which becomes perennial.

Fabricant and Perlstein[63] studied the hydrogen ion concentration of nasal secretions *in situ*, for infants and children, and noted that normal nasal secretion *in situ* has a pH ranging from 5 to 6.7; in those with acute rhinitis, 7 to 8; while in subsiding rhinitis the pH drops to 6.7 or to 7.2. In active allergic rhinitis the pH is from 7.2 to 7.3, while in subsiding allergic rhinitis the pH drops to 6.7. It is supposed that normal nasal secretion possesses the purposeful acid barrier against growth of pathogenic bacteria. The authors suggested that pediatric nasal medication possesses a pH value within the range of 5 to 6.7.

In the Queries and Minor Notes of *JAMA*,[140] a question was asked as to the value of air conditioning in pollen allergy. The consultant who answered discussed the results of Rappaport, Nelson and Welker, who found that the results from air filtration with or without cooling are unfortunately disappointing as regards asthma. The symptoms of pollenosis are completely relieved while in the room, but recur in fifteen to forty-five minutes after the patient leaves the room. The symptoms require residence in an air-filtered room for several days before relief is obtained, and asthma will recur if the patient is exposed to pollen for a very short period subsequently. Therefore, it is necessary for the patient to remain in the air-filtered room constantly to afford good relief from pollenosis and asthma. Patients who respond to hyposensitization will be much more comfortable and will be free of residual symptoms if the sleeping quarters are free from pollen.

PSYCHODYNAMICS

We have noted with interest the increase in the number of articles dealing with psychosomatic aspects of hay fever and asthma. Abramson,[3] in his article "Psychosomatic Aspects of Hay Fever and Asthma," points out that early observers in the 18th century called attention to type of symptoms associated with the blooming of the rose. The first type was associated *not* with the presence of the rose,

but actually with the time of blooming of the rose. These observations are as true today as they were then; first, specific relationship to an allergen, and secondly, incidents associated with the time the allergen is present, not necessarily specific in itself. Abramson, whose scientific acumen cannot be questioned, believes in a closer co-operation between men associated with psychosomatic medicine and allergies, and also the need of systematic postgraduate instruction in psychodynamics.

Clark[40] points out that allergy plays an important part in childhood neuroses; therefore, a problem child can be an allergic.

Haiman[82] calls attention to the fact that before success can be gained in treating an allergic person, his personality should be considered, and an insight into his problems evaluated in the light of his allergic treatments.

Miller and Baruch[131] call attention to a study of psychosomatic factors affecting allergies, including hay fever. Evidence of maternal rejection in sixty-two out of sixty-three clinical allergies is noted, as well as over-protection in thirty-six children.

Mitchell, Curran, and Myers,[132] in a study involving an analysis of recorded history interviews, with reference to personality factors in allergic nasal disorders, noted statements revealing feelings of confusion, conflict, hostility, rejection of self by others, social maladjustment, escape, dependency, fear or unhappiness.

Schutzbank,[156] in explaining the influence of climatotherapy for allergic diseases, associated possible psychosomatic influence on patients that have been relieved by change of climate; also a change of climate eliminates offending allergens.

Shure and Harris,[164] in their article, "The Neuropsychiatric Factor In Allergic Diseases," point out that in addition to the allergic factors, emotional states and psychic stimuli are introduced as integral parts of every case. The adoption of the term "intrinsic" for the neuropsychiatric factors, and "extrinsic" for the organic factors in the production of allergic disease is suggested.

REVIEWS

Salmon,[155] in a general review of the "Present Aspects of Allergy," said, "To know allergy is to know medicine." This is becoming ever apparent. Burnet[33] of Australia, in his article, "The Basis of Allergic Disease," reviews the generally accepted concepts of allergy, as related to hay fever. A number of other writers have included hay fever in their excellent reviews. Harley[91] of Australia writes with special reference to aural manifestations; Burrage,[34] with reference to new types of therapy; Lowell,[119] with emphasis on avoidance of constitutional reactions; Sutherland[174] of Australia, with special reference to the nose. The membership of the New Jersey Allergy Society[92] report in their state journal a panel discussion of the entire problem. Matas[127] of Brazil, in reviewing the results of pollen therapy, followed the generally accepted North American ideas on this subject.

NEW BOOKS

This year's outstanding book, dealing with this subject matter is Vaughan's[199] "Practice of Allergy," second edition, which has been completely revised and rewritten by Black. Harold Abramson[194] in his book, "Psychodynamics and the Allergic Patient," has a chapter on the psychosomatic aspects of hay fever and asthma prior to 1900. This was very interesting reading, showing that physicians were aware of emotional factors long before "psychosomatics" became popular. Other books dealing with the hay fever subject are: Gasio and Collicelli,[197] "T'asmo bronchiale dal punto d vista neuro-vegetatino;" Pulay and Lansel,[198] "Constitutional Medicine, Endocrinology and Allergy;" Boscolo,[195] "Asma e catarri costituzionali," and Vintinure and Marrill,[200] "Hay Fever Studies in New Hampshire, 1947."

Forman's compendium,[106] "Directory of Physicians Interested in Allergy," lists a great number of physicians interested in this subject and should prove very useful to those whose patients move or travel.

A new journal, "Acta Allergologica"[5] on the general subject of allergy is very interesting and should prove helpful in bringing us in closer contact with the north countries of Europe.

Those who have recently become interested in allergy, and want to acquaint themselves with an excellent short history of hay fever, should read Clarke's[39] "The Beginnings of Allergy; a Reminiscence."

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REFERENCES

1. Aaron, T. H., and Criep, L. H.: Neohetramine and Thephorin; two new antihistaminic drugs. Canad. M. A. J., 59:438, (Nov.) 1948.
2. Abramson, Harold A.: Psychodynamics and the allergic patient. Quart. Rev. Allergy, 3:71, (March) 1949. Abs.
3. Abramson, Harold A.: Psychosomatic aspects of hay fever and asthma prior to 1900. Ann. Allergy, 6:110-121, (March-April) 1948.
4. Abramson, Harold A.: Psychodynamics and the allergic patient. Ann. Allergy, 6:219, (May-June) 1948.
5. Acta Allergologica. Ann. Allergy, 6:626, (Sept.-Oct.) 1948.
6. Alemany-Vall, Roman: Rhinitis and asthma caused by pollen. An. med., Barcelona, 34:1-6, 1947.
7. Alexander, H. L.; Johnson, Mary C., and Bukantz, Samuel C.: Studies on correlation between symptoms of ragweed hay fever and titer of thermostable antibody. J. Allergy, 19: 1-9, 1948.
8. Alford, R. I.: Allergy in Japan. Acta allerg., Kbh., 1:232, 1948.
9. Alford, R. I.: Allergy in Japan. J. Allergy, 19:240, (July) 1948.
10. Alonso, L.; Adams, M., et al.: Mode of action of antihistaminic agents. Federation Proc., 7:202, (Mar.) 1948.
11. Alperstein, Bernard B.: Bromothen and Chlorothen: 5-brom-2-thenyl and 5-chlor-2-thenyl derivatives of the ethylenediamine group. Ann. Allergy. 6:439, (July-Aug.) 1948.
12. Andrews, T. Gaylord: Statistical studies in allergy. II. A factorial analysis. J. allergy, 19:43-47, 1948.
13. Arbesman, Carl E.: Comparative studies of several antihistaminic drugs. J. Allergy, 19: 178, (May) 1948.
14. Becker, Elmer L.: Quantitative studies in skin testing. I(A). The assay of ragweed extracts by means of scratch test utilizing an "all or none" response. J. Allergy, 19:100-108, 1948.
15. Becker, Elmer L.: Quantitative studies in skin testing. I(B). The graphic solution of the assay of ragweed extracts by means of scratch test utilizing an "all or none" response. J. Allergy, 19:108-118, 1948.
16. Becker, Elmer L., and Rappaport, B. Z.: Quantitative studies in skin testing. II. The form of the dose-response curve utilizing a quantitative response. J. Allergy, 19:317-329, 1948.
17. Becker, Elmer L., and Rappaport, [illegible] studies in skin testing. III. The assay of the direct skin reactivity of [illegible] tracts by endermal testing utilizing an "all or none" response. J. Allergy, [illegible]
18. Bernstein, Theodore, and Feinberg, [illegible] antagonists. XLL. Neohetramine. Clinical and pharmacologic results. [illegible] 1948.
19. Black, J. H.: Influence of respiratory allergy upon the life and health of the individual. J. Insur. M., 3:34, (July-Aug.) 1948.
20. Blackman, Norman S., Haye, James C.: Fatality associated with Benadryl therapy. J. Allergy, 19:390, 1948.
21. Blumstein, George I., M.D., et al: The ragweed extermination plan for Philadelphia. Pennsylvania Med. J., 52:39, 1948.
22. Bonnevie, P.: The diagnostic and clinical importance of the skin test. Acta allerg., Kbh., 1:167-83, 1948.
23. Boyd, Linn, J.; Weissberg, Jonas, and McGavack, Thomas H.: Tolerance studies of the antihistaminic drug, Thephorin. New York State J. Med., 48:1596-8, 1948.
24. Bowen, Ralph: Experience with hay fever "X" during the year of 1948. Letters, Internd. Corr. Soc. Allergy, 11:139.
25. Brown, B. B., and Werner, H. W.: The pharmacologic properties of 2-(alpha-2-dimethylaminowthoxy [illegible] succinate, a new antihistaminic agent. J. Lab. & Clin. Med., [illegible]
26. Brown, Barbara B., and Werner, Harold W.: The effects of Decapryn Succinate, a new antihistamine agent, in some natural and acquired hypersensitivities in animals. Ann. Allergy, 6:122, (Mar.-Apr.) 1948.
27. Brown, E. A.: A clinical evaluation of a new antihistamine agent, Trimeton. Ann. Allergy, 6:393-7, (July-Aug.) 1948.
28. Brown, Ethan Allan; Weiss, L. Robert, and Maher, Joseph P.: The clinical evaluation of a new histamine antagonist, Decapryn. Ann. Allergy, 6:1-6, (Jan.-Feb.) 1948.
29. Brown, Earl B., and Brown, Frederick W.: The use of a new antihistaminic combination in the treatment of allergic disorders. New York State J. Med., 48:1465, (July 1) 1948.
30. Brown, Halla, and Loveless, Mary Hewitt: Allergenic (skin-test) activity of low ragweed pollen after irradiation of extract with ultraviolet light. Ann. Allergy 6:7-10, (Jan.-Feb.) 1948.
31. Brown, S. F.: Side reactions to Pyribenzamine medication. Proc. Soc. Exper. Biol., 67:373, (Mar.) 1948.
32. Bukantz, Samuel C.; Johnson, Mary C., and Hampton, Stanley: Quantitative immunologic studies with allergens. I. Colorimetric absolute methods in the analysis of factors influencing precipitation of ragweed pollen extracts and homologous rabbit antisera. Fifth annual meeting of the Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.

33. Burnet, F. M.: The basis of allergic disease. M. J. Australia, 1:29-35, (Jan. 10) 1948.
34. Burrage, Walter L.: Allergy. New England J. Med., 238:770-775, (May 27) 1948. Recent therapeutic trends in allergy. Ibid, 238:181-184, 1948.
35. Calder, A. G. S.: Antihisan in the treatment of allergic rhinitis. Lancet, 1:863, (June 5) 1948.
36. Campbell, Berry: Inhibition of anaphylactic shock by acetylsalicylic acid. Science, 108: 478-79, 1948.
37. Campbell, Dan H.: The immunochemical aspects of allergy. J. Allergy, 19:151-160, 1948.
38. Chen, G.; Bratton, A. A., Jr., and Ensor, G.: The joint antihistaminic effect and acute toxicity of Adrenalin and Benadryl HCl. Federation Proc., 7:211, pa. 1, (Mar.) 1948.
39. Clarke, T. W.: The beginnings of allergy; a reminiscence. Ann. Allergy, 6:378-85, (July-Aug.) 1948.
40. Clarke, T. W.: The part of allergy in childhood neuroses. J. Child Psychiat., 1: sect. 2, 177-80, 1948.
41. Claus, E. P.: A study of the anemophilius plant of Puerto Rico. Bot. Gaz., 109:249-258, 1948.
42. Cohen, M. B., and Abram, L. E.: Growth patterns of allergic children. Acta allerg., Kbh., 1:225, 1948.
43. Cohen, Milton B., and Abram, Lewis E.: Growth patterns of allergic children. J. Allergy, 19:165-172, 1948.
44. Cohen, E. B.; Davis, H. P., and Mowry, W. A.: Thephorin in allergy; a study of 292 cases. Am. J. Med., 5:44-47, (July) 1948.
45. Cohen, E. N., and Van Bergen, F.: Isuprel, a new bronchodilating agent. Bull. Univ. Minnesota Hosp., 19:424-34, (May 7) 1948.
46. Criep, L. H.: Practical aspects of allergic rhinitis. J.A.M.A., 136:601-604, 1948.
47. Criep, L. H., and Aaron, T. H.: Thephorin; an experimental and clinical evaluation in allergic states. J. Allergy, 19:304-12, (Sept.) 1948.
48. Criep, L. H., and Aaron, T. H.: Neohetramine: an experimental and clinical evaluation in allergic states. J. Allergy, 19:215-24, (July) 1948.
49. Current Med. Digest, (May) 1948: Are antihistamine drugs safe for aviation personnel?
50. Curry, J. J.: Comparative action of acetyl-beta-methyl choline and histamine on the respiratory tract in normals, patients with hay fever, and subjects with bronchial asthma. J. Clin. Investigation, 26:430, 1947.
51. Curry, John J.; Fuchs, J. E., and Leard, S. E.: Clinical and experimental studies with Orthoxine in the treatment of bronchial asthma. Fifth annual meeting of the Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
52. Dole, H.: Antihistaminic substances. Brit. M. J., 2:281-3, (Aug. 7) 1948.
53. Dreyfus, P., and Schwartz, M.: The absorption and circulation of antigen, elucidated by transfusion experiments. Acta allerg., Kbh. 1:114-9, 1948
54. Deppe, Edwin F.: Hay fever pollens in the Seattle area. Northwest Med., 47:439-441, (June) 1948.
55. Doyle, G.: Nasal desensitization in allergy. M. J. Australia, 2:94-97, (July 24) 1948.
56. Dubois de Montreynaud, J. M.: Treatment of hay fever. Gaz. méd. de France, 55:337, 1948.
57. Duerfeldt, T. H.: Acute Benadryl poisoning. Northwest Med., 46:781, (Oct.) 1947.
58. Dunlop, D. M., and R. B. Hunter: Lancet, p. 849, (May 29) and p. 926, (June 12) 1948.
59. Durham, Oren C.: Airborne allergens in the national parks. Fifth annual meeting of the Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
60. Editorial: Possible dangers in mild shock therapy. Ann. Allergy, 6:597, 1948.
61. Editorial: Antihistaminic agents in allergy. Ann. Allergy, 6:62, (Jan.-Feb.) 1948.
61a. Ehrlich, Norman J., and Kaplan, M. A.: Patient's evaluation of antihistaminics. Presented before American College of Allergists' meeting, 1949. (To be published.)
62. Eisenstadt, W. S.: The incidence and significance of molds on allergic respiratory symptoms. Lancet, 68:217, 1948.
63. Fabricant, N. D., and Perlstein, M. A.: Hydrogen ion concentration of nasal secretion in situ in infants and children. Arch. Otolaryng., 47:765, 1948.
64. Fanburg, S. J.: Pyribenzamine fever (case report). J. M. Soc. New Jersey, 45:392, (Aug.) 1948.
65. Farmer, Laurence: Experiments on histamine refractoriness. III. The effect of histamine pretreatment on the establishment of active sensitization. J. Allergy, 19:358, 1948.
66. Farmer, Laurence: Experiments on histamine refractoriness. IV. Histamine pretreatment in eggwhite-sensitized guinea pigs. J. Allergy, 19:361, 1948.
67. Feinberg, S. M.: Antihistaminic drugs: pharmacology and therapeutic effects. Am. J. Med., 3:560, (Nov.) 1947.
68. Feinberg, S. M., and Bernstein, T. B.: Histamine antagonists; a new antihistaminic drug; experimental and clinical results. J. Lab. & Clin. Med., 33:319-24, (Mar.) 1948.
69. Feinberg, Samuel M.; Bernstein, Theodore B.; Rose, Jack M.; Feinberg, Alan R., and Friedlaender, Sidney: Antihistaminic drugs. J.A.M.A., 137:281, (May 15) 1948.
70. Fenton, Meryl M., and Huffman, Elston R.: Iontophoresis of Pyribenzamine Hydrochloride in nasal allergy. Fifth annual meeting of the Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
71. Flensborg and Samsoe-Jensen, T.: Mold spore counts in outside air in Copenhagen. Acta Allerg., Kbh., 1:194-13, 1948.
72. Flensborg, E. W., and Samsoe-Jensen, T.: Mold spore counts in outside air in Copenhagen. Acta Allergologica, 1:104, 1948.
73. Findeisen, D. J. R.: Pervitin treatment of hay fever. Med. Klin., 42:593, 1947.
74. Frank, R.: Study of a new histamine antagonist. Ann. Allergy, 6:398-404, (July-Aug.) 1948.
75. Friedlaender, Alex S., and Friedlaender, Sidney: An evaluation of Antistine, a new antihistaminic substance. Ann. Allergy, 6:23, (Jan.-Feb) 1948.
76. Fuchs, A. M.; Schulman, P. M., and Strauss, Margaret B.: Clinical studies in Pyribenzamine in hay fever. J. Allergy, 18:385, (Nov.) 1947.
77. Gay, L. N.; Landau, S. W., et al: Comparative study of antihistamine substances; clinical observations. Bull. Johns Hopkins Hosp., 83:356-65, (Oct.) 1948.
78. Gilman, Alfred: The pharmacology of drugs used in allergic conditions. J. Allergy, 19: 281-288, 1948.
79. Gottlieb, Philip, M.: No ragweeds in the British Isles. Correspondence, J.A.M.A., 136: 490, 1948.
80. Greco, J. B., and Bartos, M. P.: Pollen allergy; counting of pollen in air in city of Santos. Brazil Med., 61:434-35, (Dec. 20-27) 1947.
81. Gutmann, M. J.: Allergic warm season conjunctivitis. Acta med. Orient., 6:167, 1947.

82. Haiman, J. A.: The psychosomatic approach to the treatment of allergy, bronchial asthma, and systemic disorders. M. Rec., 161:467-73, (Sept.) 1948.
83. Haley, T. J.: The antihistaminic drugs; a review of the literature. J. A. Pharm. A., 37: 383-408, (Oct.) 1948.
84. Halpern, Bernard: Recent researches on synthetic antihistaminics. Foreign Letters, J.A.M.A., 136:841, (March 20) 1948.
85. Halpern, B. N. [illegible]: A new synthetic antihistamine substance derived from phenothiazine; [illegible]. A. J., 59:322-6, (Oct.) 1948.
86. Halpin, L. J.: [illegible] a review of recent literature. Ann. Allergy, 6:600-17, (Sept.-Oct.) 1948.
87. Hampton, Stanley F.; Bukantz, Samuel C., and Johnson, Mary C.: Quantitative immunologic studies with allergens. II. Fifth annual meeting of the American Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
88. Hansel, French K.: The diagnosis and treatment of hay fever with particular reference to the ragweed type. Laryngoscope, 58:380-95, 1948.
89. Hansel, French K.: The treatment of headache—with particular reference to the use of Cafergone (Ergotamine tartrate and caffeine) for the relief of attacks. Ann. Allergy, 6:2, 157-158, (March-April) 1949.
90. Harley, D.: Diagnosis and treatment of hay fever. M. Press, 219:486-488, (June 2) 1948.
91. Harley, D.: Some observations on the fundamentals of allergy with special reference to its aural manifestations. J. Laryng. & Otol., 62:1-10, (Jan.) 1948.
92. Hay fever. J. M. Soc. New Jersey, 45:389, (Aug.) 1948.
93. Heise, Herman A., and Heise, Eugenia R.: The distribution of ragweed pollen and Alternaria spores in the upper atmosphere. J. Allergy, 19:403, 1948.
94. Henson, G. E.: Specific treatment of pollenosis. J. Florida M. A., 35:28-29, (July) 1948.
95. Herxheimer, H.: Antihistamine drugs. Brit. M. J., 1:4559, (May 22) 1948.
96. Herxheimer, H.: Aleudrine and Anthisan in bronchial spasm. Lancet, 1:926, (June 12) 1948.
97. Hill, Lewis Webb: Food sensitivity in 100 asthmatic children. New England J. Med., 238: 657-659, (May 6) 1948.
98. Hill, Lewis Webb: Pollen sensitivity in 100 asthmatic children. New England J. Med., 239:1039, 1948.
99. Holtkamp, Dorsey; Hagerman, Dwnia, and Whitehead, Richard: Side effects of three antihistaminic drugs. J. Allergy, 19:384, 1948.
100. Hudson, A. L.: Antistine (imidazole derivatives) clinical trials. Canad. M. A. J., 58: 166-168, (Feb.) 1948.
101. Hughes, R. F.: Clinical experiences with Antistine. Ann. Allergy, 6:405-7, (July-Aug.) 1948.
102. Jennes, S. W.: Seasonal hay fever. Connecticut M. J., 12:705-10, (Aug.) 1948.
103. Juhlin-Dannfelt, C.: About the occurence of various forms of pollen allergy in Sweden. Acta Med. Scandinav., 131:563-77, (July 12) 1948.
104. Kaplan, Morris A., and Ehrlich, Norman J.: A clinical evaluation of a new antihistaminic drug, Antistine. Ann. Allergy, 6:697, (Nov.-Dec.) 1948.
105. Kaplan, Morris A., and Ehrlich, Norman J.: Progress in allergy. Hay fever. Ann. Allergy, 6:323, (May-June) 1948.
105a. Kaplan, M. A., and Ehrlich, Norman J.: International Corr. Soc. of Allergists, Series XI:75.
106. Khellin. J.A.M.A., 137:758, (June 19) 1948.
107. Kierland, R. R., and Patten, Robt. T.: An evaluation of Thenylene. Proc. Staff Meet. Mayo Clin., 23:48-51, (Jan. 21) 1948.
108. Kleckner, M. A., Jr.: Clinical appraisal of Benadryl, Pyribenzamine and Anthallan in treatment of allergic disorders. Ann. Int. Med., 28:583-597, (March) 1948.
109. Krasno, L. R.; Grossman, M., and Ivy, A. C.: The inhalation of novisodrin sulfate dust. Aleudrine. Science 108:476-478, (Oct. 29) 1948.
110. Krueger, A. A.: Histamine in treatment of allergic diseases. Northwest Med., 47:27-29, (Jan.) 1948.
111. Landau, S. W., and Gay, L. N.: Comparative study of antihistamine substances; introduction and Dale experiments. Bull. Johns Hopkins Hosp., 83:330-42, (Oct.) 1948.
112. Landau, S. W.; Mariott, J. L., and Gay, L. N.: Comparative study of antihistamine substances; activity in vivo against histamine intoxication and anaphylactic shock of guinea pigs. Bull. Johns Hopkins Hosp., 83:343-55, (Oct.) 1948.
113. Lehman, G.: Pharmacologic properties of new antihistamine, Thephorin and derivatives. J. Pharmacol. & Exper. Therap., 92:249-59, (March) 1948.
114. Levin, Louis; Kelly, John F., and Schwartz, Emmanuel: A clinical evaluation of Neo-Antergan and Antistine in the treatment of ragweed hay fever. New York State J. Med., 48:1474, (July 1) 1948.
115. Lewi, G. G.: Asthma and hay fever, a different concept. Clin. Med., 54:402-405, 1947.
116. London, M.: Initial symptoms of pollenosis at an advanced age. Ohio State M. J., 44:489, 1948.
117. Loveless, M. H.: Adjuvant treatment of hay fever with emulsions of pollen extract. Acta Allerg., Kbh., 1:226, 1948.
118. Loveless, Mary H., and Brown, Halla: Comparison between clinical effects of PBZ and those of Benadryl. New England J. Med., 237:501, (Oct. 2) 1947.
119. Lowell, F. C.: The treatment of allergic diseases. M. Clin. North America, 32:1369-76 (Boston number), (Sept.) 1948.
120. Lowell, Francis C., and Schiller, Irving W. Measurement of changes in vital capacity as a means of detecting pulmonary reactions to inhaled aerosolized allergenic extracts in asthmatic subjects. J. Allergy, 19:100-107, 1948.
121. Lubowe, Irwin L.: Delayed reaction to penicillin treated with Thephorin. New York State J. Med., 48:1505, (July 1) 1948.
122. Macht, D. I., and Hoffmaster, T.: Influence of Benadryl and Pyribenzamine on the neuromuscular system of rats. Federation Proc., 7: pt. 1, 242, (Mar.) 1948.
123. Mackmull, Gulden: The influence of intravenously administered Benadryl on blood pressure and electrocardiogram. J. Allergy, 19:365, 1948.
124. Marchand, A. M.: Hay fever plants of Puerto Rico. Bol. Asoc. med. Puerto Rico, 40: 30-33, (Jan.) 1948.
125. Markow, Harry; Bloom, Samuel, and Leibowitz, H.: An evaluation of Hydryllin in the symptomatic treatment of allergy. New York State J. Med., 48:2390-2392, 1948.
126. Marsh, D. F.: The pharmacology of the antihistaminic agents. West Virginia M. J., 44:10, 265-9, (Oct.) 1948.
127. Matas Pons, J.: Consideraciones sobre los resultados del tratonmento desensitizante en la polenosis. An. méd. Barcellona, 35:104-9, 1948.

128. McGavack, T. H.; Schulman, P. M., et al.: Ann. Allergy, 19:141-145, (March) 1948.
129. McGavack, T. H.; Drekter, I. J., et al.: Levels for Pyribenzamine and Benadryl in blood and urine following a single orally administered dose. J. Allergy, 19:251-5, (July) 1948.
130. McGrath, R. J.: Vasomotor rhinitis and homeopathic treatment. J. Am. Inst. Homeop. 41:211-3, (Oct.) 1948.
131. Miller, H., and Baruch, D. W.: Psychosom. Med., 10:275-278, (Sept.-Oct.) 1948.
132. Mitchell, J. H.: Curran, C. A., and Myers, R. N.: Personality factors in allergic nasal disorders. Acta Allerg., Kbh. 1:231, 1948.
133. Mitchell, W. F.; Sivon, I., and Mitchell, J. H.: Vulvo-vaginal pruritus associated with hay fever. Ann. Allergy, 6:144, 1948.
134. Modern, F. W. S.: Antibody formation. Ann. West. M. & S., 2:432, (Sept.) 1948.
135. Newton, Ann. Scherago, M., and Weaver, R. H.: Mold distribution in air and dust in Kentucky. Ann. Allergy, 6:260, (May-June) 1948.
136. Peters, John: Thephorin, a new antihistaminic. Illinois M. J., 93:314-318, (June) 1948.
137. Pharmacy and Chemistry, Council on: Council report on Aleudrine Sulfate. J.A.M.A., 138:888, 1948.
138. Poupa, O.: Effect of antihistamines on daphnia. Nature, 161:235, (Feb. 14) 1948.
139. Queries and Minor Notes: Allergic rhinitis. J.A.M.A., 137:570, 1948.
140. Queries and Minor Notes: Pollen allergy. J.A.M.A., 137:18, 1940.
141. Queries and Minor Notes: Effect of Benadryl on pregnancy. J.A.M.A., 136:359, (Jan. 31) 1948.
142. Queries and Minor Notes: California pollens. J.A.M.A., 139:554, 1949.
143. Queries and Minor Notes: Use of Hapamine and the antihistaminic drugs. J.A.M.A., 136: 592, (Feb. 21) 1948.
144. Queries and Minor Notes: Antihistaminic drugs. J.A.M.A., 139:419, 1949.
145. Reinhard, J. F.; Scudi, J. V., et al.: Pharmacological characteristics of Neobetramine. Proc. Soc. Exper. Biol., 66:512-6, (Dec.) 1947.
146. Reuse, J. J.: Comparisons of various histamine antagonists. Brit. J. Pharm., 3:174-80, (June) 1948.
147. Reymann, F., and Schwartz, M.: House dust and fungus allergy. Acta path. et microbiol. Scandinav., 24:76, 1947.
148. Robbins, Kenneth C.; Samuels, Arthur, and Mosko, Milton M.: Chemical studies on a skin-reactive fraction from short ragweed pollen. J. Allergy, 19:35-43, 1948.
149. Rockwell, G. E.: Histamine derivatives with prolonged action. Ann. Allergy, 6:353-7, (July-Aug.) 1948.
150. Rooks, Roland: A device for the electrostatic precipitation of bacteria and fungus spores upon culture plates. J. Allergy, 19:200-206, 1948.
151. Rooks, Roland: A device for the electrostatic precipitation of pollen and fungus spores upon a counting slide. J. Allergy, 19:206-209, (May) 1948.
152. Rowe, P., and Sheldon, J. M.: Synthetic diets; their use as a diagnostic procedure in allergic disease. J. Lab. & Clin. Med., 33:1059-67, (Sept.) 1948.
153. Sachs, B. A.: The toxicity of Benadryl; report of a case and review of the literature. Ann. Int. Med., 29:135-44, (July) 1948.
154. Salen, E. B.: The diagnostic and clinical importance of the skin test. Acta Allerg., Kbh., 1:127-66, 1948.
155. Salmon, P.: Present-day aspects of allergy. Brooklyn Hosp. J., 6:207-12, (Oct.) 1948.
156. Schutzbank, F. B.: Clinical aspects of climatotherapy for allergic diseases. Acta Allerg., Kbh., 1:224, 1948.
157. Schwartz, Emanuel, and Leibowitz, Harry: Local nasal therapy with Pyribenzamine in seasonal and nonseasonal hay fever. Fifth annual meeting of the American Academy of Allergy, Atlantic City, N. J., 1948.
158. Scudi, John V., and Reinhard, John F.: Pharmacologic characteristics of Neobetramine, a new antihistaminic drug. J. Allergy, 19:184, (May) 1948.
159. Seltzer, A.: Convulsions following epinephrine. Report of a case. Ann. Allergy, 6:153, 1948.
160. Serafini, U.: Studies on histamine and histamine antagonists. J. Allergy, 19:256-70, 1948.
161. Serafini, U., and Biozzi, G.: The histamine blood equivalent after physical efforts in normal people and in cases of hay fever. Clin. Nuova, 312:357-62, 1946.
162. Sbeldon, J. M.; Weller, K. E., et al.: Clinical observations with Decapryn; a new antihistaminic compound. Univ. Hosp. Bull., Ann Arbor, 14:13-5, (Feb.) 1948.
163. Shulman, Maurice H.: The use of ragweed ointment in determining seasonal variation of ophthalmic sensitivity. Fifth annual meeting of the American Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
164. Shure, N., and Harris, M. C.: The neuropsychiatric factor in allergic disease. M. Arts & Sc., 2:119-123, (Oct.) 1948.
165. Simon, S. W.: Nethaphyl in bronchial asthma. Ann. Allergy, 6:662, (Nov.-Dec.) 1948.
166. Southwell, N.: "Anthisan" (Neo-Antergan malleate). Brit. M. J., 1:877-880, (May 8) 1948.
167. Spain, W. C., and Pflum, F. A.: An evaluation on the present status of antihistaminic substances. New York State J. Med., 48:2272-2275, 1948.
168. Starr, M. P., and Rankin, R. M.: Acute Benadryl intoxication: case report. Northwest Med., 47:195, (Mar.) 1948.
169. Stavraky, G. W.: Potentiation of the effect of antihistaminic agents by iron compounds. Federation Proc., 7: pt. 1, 257, (Mar.) 1948.
170. Sternberg, Louis, and Gottesman, James: Clinical observations with Thephorin, a new antihistaminic drug. Ann. Allergy, 6:569, (Sept.-Oct.) 1948.
171. Strauss, M. H.: Eczematous contact-type allergy to Pyribenzamine. J. Invest. Dermat., 11:155, (Sept.) 1948.
172. Strebel, J.: Behandlung der Pollen-Allergie im aktiven und inaktiven Stadium. Schweiz. med. Wchnschr., 78:879-81, (Sept. 11) 1948.
173. Suer, W. J.: A chemical concept of immunity. Ann. Allergy, 6:564-8, (Sept.-Oct.) 1948.
174. Sutherland, C.: Allergic diseases and the nose. Med. J. Australia, 2:513-7, (Oct. 30) 1948.
175. Targow, A. M.: Pollen survey of Los Angeles, 1941-1945. Ann. Allergy, 6:645-54, (Nov.-Dec.) 1948.
176. Tomlinson: Hay fever to eczema via Benadryl. Brit. M. J., 1:276, (Feb. 7) 1948.
177. [illegible] J. Allergy, 19:280-291, (Sept.) 1948.
178. [illegible] K. J., et al.: Pharmacology of a new antihistamine, B-pyr- [illegible] Therap., 94:197-208, (Oct.) 1948.
179. Vander Brook, M. J.; Olson, K [illegible] r., and Kuizenga, M. H.: Pharmacology of new antihistamine, Pyr [illegible] & Exper. Therap., 94:2-197, (Oct.) 1948.

180. Veldee, Milton V.: Specifications recommended as guides in the collection and preservation of pollens. J. Allergy, 19:210-214, 1948.
181. Waldbott, George L.: Clinical evaluation of Neohetramine, a new antihistamine. Ann. Allergy, 6:305, (May-June) 1948.
182. Waldbott, G. L., and Young, M. I.: Antistine, Neo-Antergan, Neohetramine, Trimeton, and antihistaminic RF-3277; and appraisal of their clinical value. J. Allergy, 19:313-6, (Sept.) 1948.
183. Walzer, Abraham, and Golan, Harry: Evaluation of electrophoretic method of skin testing. Fifth annual meeting of the American Academy of Allergy, Atlantic City, N. J., (Dec. 6-9) 1948.
184. Walzer, E. H.; Siegel, B. B.; Chait, R. A., and Walzer, M.: Survey of ragweed pollination in the New York metropolitan district in 1947. New York State J. Med., 48:2019, 1948.
185. Walzer, E. H.; Sherman, J.; Chait, R. A., and Walzer, M.: Survey of ragweed pollination in the New York metropolitan district in 1946. New York State J. Med., 47:1979, 1947.
186. Weiss, W. I., and Howard, R. M.: Antihistamine drugs in hay fever; a comparative study with other therapeutic methods. J. Allergy, 19:271-7, (July) 1948.
187. Wine, M. B.: The X-hay fever problem of the south. J. M. A. Georgia, 37:227-228, (June) 1948.
188. Winter, Charles A.; Kuna, Samuel, and Mushett, C.: Studies on the chronic toxicity of Pyranisamine Maleate (Neo-Antergan Maleate) in animals. J. Allergy, 19:371, 1948.
189. Winter, C. A.: The potentiating effect of antihistaminic drugs upon the sedative action of barbiturates. J. Pharmacol. & Exper. Therap., 94:7-11, (Sept.) 1948.
190. Wittich, F. W.: Trimeton in the treatment of allergic diseases. Ann. Allergy, 6:497, (Sept.-Oct.) 1948.
191. Wittich, F. W.: A clinical evaluation of Orthoxine in the treatment of allergic diseases. Ann. Allergy, 6:664-6, (Nov.-Dec.) 1948.
192. Wodehouse, R. P.: Patterns of allergic sensitization. Ann. Allergy, 6:358-77, (July-Aug.) 1948.
193. Wolf, A.: A fall-pollinating red berry juniper. Ann. Allergy, 6:431-4, (July-Aug.) 1948.

NEW BOOKS

194. Abramson, H.: Psychodynamics and the Allergic Patient. Saint Paul: Bruce Publishing Company, 1948
195. Boscolo, Bragadin R.: Asma e catarri costituzionali.
196. Forman, J.: Comp. Directory of Physicians Interested in Allergy.
197. Gasio, R., and Collicelli, A.: L'asma bronchiale dal punto di vista neuro-vegetativo.
198. Pulay, E., and Lansel, P., editors: Constitutional Medicine, Endocrinology and Allergy.
199. Vaughan, W. T.; Revised by J. Harvey Black; Practice of Allergy. 2nd ed. St. Louis: The C. V. Mosby Co., 1948.
200. Vintinnre, F. J., and Marrill, G. W., Jr.: Hay-fever Studies in New Hampshire, 1947. Vol. II, III, IV.

SENSITIVITY TO KELCOLOID

(Continued from Page 682)

individuals without an allergic history and without a familial background of allergy. Kelcoloid is apparently a preparation of low allergenicity, but clinical sensitivity has been demonstrated.

SUMMARY

Although human hypersensitivity, together with the production of allergic symptoms, can occur with Kelcoloid, it must be assumed to have a minor place among the substances responsible for allergic manifestations. It is probably, therefore, a good substitute for such preparations as the water-soluble gums, namely, karaya, locust bean, acacia, tragacanth and Irish moss extract.

REFERENCES

1. Feinberg, S. M., and Schoenkerman, B. B.: Wisconsin M. J., 39:734, 1940.
2. Figley, K. D.: J.A.M.A., 114:747, (March) 1940.
3. Ouer, Roy A., Evans, H. M., and Lepkovsky, S.: J. Biol. Chem., 5:108, 1935.

News Items

HANSEL FOUNDATION

The Hansel Foundation held a panel discussion on Friday, October 7, just preceding the annual meeting of the American Academy of Ophthalmology and Otolaryngology at the Palmer House, October 9-14. Dr. French K. Hansel was the moderator, and the program of the panel discussion was as follows:

Morning Session—9:00 A.M.

I. OTOLARYNGOLOGIC DIAGNOSIS OF ALLERGY.

1. Office Management.....W. Byron Black, M.D., Kansas City, Mo.
2. Symptomatology and Manifestations. Edward King, M.D., Los Angeles, Calif.
3. Cytology.....William H. Craddock, M.D., Cincinnati, Ohio
4. Pathologic Changes on the Tissue. X-Ray Diagnosis.....
.....Geo. E. Shambaugh, Jr., M.D., Chicago, Ill.

II. THE ALLERGIC INVESTIGATION.

1. Etiologic Factors.....F. Lambert McGannon, M.D., Lakewood, Ohio
2. History Taking in Allergy.....Joseph W. Hampsey, M.D., Pittsburgh, Pa.
3. Skin Testing.....Geo. E. Shambaugh, Jr., M.D., Chicago, Ill.
4. Prophylaxis—Avoidance or Elimination of Allergens.....
.....Eugene L. Derlacki, M.D., Chicago, Ill.

III. TREATMENT.

1. Disposition of Patient, Plan of Treatment.....
.....French K. Hansel, M.D., St. Louis, Mo.
2. Dust Therapy.....Rea E. Ashley, M.D., San Francisco, Calif.
3. Pollen Therapy.....Michael H. Barone, M.D., Buffalo, N. Y.

Luncheon—12:00 Noon

Afternoon Session—2:00 P.M.

IV. TREATMENT (Continued)

1. Dietary Manipulation and Nutrition.....
.....A. G. Rawlins, M.D., San Francisco, Calif.
2. Drugs.....Walter E. Owen, M.D., Peoria, Ill.
3. Indications for Surgery.....Kenneth L. Craft, M.D., Indianapolis, Ind.

V. HEADACHES, VERTIGO, ALLERGY OF THE EAR.

1. Histaminic Cephalgia.....French K. Hansel, M.D., St. Louis, Mo.
2. Tinnitus.....Howard P. House, M.D., Los Angeles, Calif.
3. Allergy and Deafness.....Hugh A. Kuhn, M.D., Hammond, Ind.
4. Summary of Allergy and the Ear....Gösta Dohlman, M.D., Lund, Sweden

VI. OCULAR ALLERGY.

1. General Considerations.....W. Byron Black, M.D., Kansas City, Mo.
2. Allergic Conjunctivitis and Contact Dermatitis.....
.....S. Albert Hanser, M.D., St. Louis, Mo.
3. Industrial Ocular Allergy.....Hedwig S. Kuhn, M.D., Hammond, Ind.
4. Ocular Allergy.....Wm. D. Gill, M.D., San Antonio, Texas

POSTGRADUATE COURSES IN ALLERGY

Columbia University announces three postgraduate courses in allergy during 1949-50, as follows:

Mt. Sinai Hospital

Medicine PM 36—Allergy. October 4-November 29, 1949; and January 24-March 27, 1950, omitting February 22. Fee $40. *J. Harkavy,* M.D. and staff.

Tuesday 9-11

Fundamentals of anaphylaxis and its relation to clinical manifestations of allergy. Newer concepts of mechanisms involved in hay fever and bronchial asthma and treatment. Food allergy and its effects on the respiratory, nervous, gastro-intestinal, and cutaneous organs. Bacterial, drug and serum hypersensitiveness.

Pediatrics PM 31—Allergy in Children. October 14-December 2, 1949. Fee $30. *M. M. Peshkin,* M.D.

Friday, 3:30-5:30

Anaphylaxis; allergy; asthma, skin and ophthalmic tests. Eczema and angioneuroses.

Roosevelt Hospital

Medicine PM 81—Clinical Allergy. October 17-28, 1949. Fee $120. *Robert A. Cooke,* M.D. and staff.

Monday through Friday, 9-1, and 2-6

This course is designed to provide internists, pediatricians, and other physicians a review of modern concepts of the theoretical and practical aspects of allergy, in relation to clinical problems. All types of allergic disease will be studied including the less common vascular and cerebral allergies. The practical work will include history taking, physical examination, skin testing by direct and passive transfer methods, and laboratory diagnosis. In the laboratory the principles of allergic extractions and standardizations and the preparation of individual extracts will be considered in a practical way. There will also be demonstrations of anaphylaxis, Dale reactions, precipitin tests, and preparation of autogenous vaccines. Maximum class, 8; minimum, 6.

SYMPOSIUM ON DERMATOLOGIC ALLERGY

An important Symposium on Itching Dermatoses will be the highlight of the program of the Sixth Annual Convention of the College from 2:00 p.m. to 5:50 p.m., Tuesday, January 17, 1950, in the Gold Room of the New Hotel Jefferson, St. Louis, Missouri. Dr. Stephan Epstein, Marshfield Clinic, Marshfield, Wisconsin, is chairman of this section. Dr. Stephen Rothman, Professor of Dermatology, University of Chicago, is the guest speaker and will present "The Physiology and Pharmacology of Pruritus." Dr. Carl Laymon, Clinical Professor of Dermatology, University of Minnesota, will discuss "The Diagnosis of Non-Allergic Itching Dermatoses." Dr. F. W. Lynch, Clinical Professor of Dermatology, University of Minnesota, will present "The Classification of Eczema, and the Psychosomatic Factors in Eczema." "The Topical Treatment of Acute and Chronic Dermatitis (Contact and Atopic), Including Antihistamanics" will be given by Dr. James Webster, Assistant Professor of Dermatology, Northwestern University. Doctor Epstein will discuss "The Treatment of Infectious Eczematoid Dermatitis," and Dr. Herbert Rattner, Associate Professor of Dermatology and Syphilology, Northwestern University, "The Treatment of Pruritus." Following a short recess, there will be a one-hour round table panel on "Itching Dermatoses" by Doctors Laymon, Lynch, Rattner, Rothman, Webster and Epstein. All dermatologists are daily encountering allergic skin disorders and they should take advantage of this great opportunity to increase their knowledge of these conditions which are of increasing importance.

BRAZILIAN SOCIETY OF ALLERGY

The ordinary meeting of the Brazilian Society of Allergy was held in conjunction with the Brazilian Society of Dermatology at the Geral Polyclinic of Rio de Janeiro on May 31, 1949. The following program was presented: (1) Conference by Prof. Francisco A. Rabelo, "Dermatologic Manifestations in Allergy." (2) Members of the two societies presented cases. At the ordinary meeting held on June 28, 1949, the following roundtable discussion was held: (1) "Etiology of Asthma" by Dr. Mario Miranda, (2) "Treatment of Asthma" by Dr. A. Oliveira Lima. These two items were followed by a discussion.

SPANISH SOCIETY OF ALLERGY

At the first Congress of the Sociedad Espanola de Alergia at Madrid, which was announced in the May-June issue of ANNALS OF ALLERGY, the Society, by action of the Congress will be known as the Spanish-Portuguese Society of Allergy. Until organized in Portugal, however, it will continue as the Sociedad Espanola de Alergia. It was also unanimously voted to accept the invitation to become an official member of the International Association of Allergists. Dr. Fred W. Wittich was one of the Honorary Members elected at this Congress. Officers elected were: President, Prof. C. Jiménez Díaz; Vice President, Dr. Francisco J. Farrerons-Co.; Secretary, Dr. Iahoz Marques; Vice Secretary, Dr. Iahoz Navarro. Other members elected to the Board were: Prof. Diaz Rubio, Cruz Auñon, Ortiz de Landazuri, Dr. R. Frouchtman, Dr. Sanchez Cuenca, and Dr. Surinyach.

The next Congress will be held in the spring of 1951 at a place to be decided later by the Board of Directors. The following assignments were made: "Influence of Climate on Allergy" to Prof. Cruz Auñon and Prof. Diaz Rubio and Dr. Farrerons; "Beginning of Asthma and its Prophylaxis" to Dr. Sanchez Cuenco; "Allergic Personality" to Prof. Ortiz de Landazuri; "Urticaria" to Dr. Frouchtman, and "Digestive-Allergy" to Dr. Surinyach.

SWISS SOCIETY OF ALLERGY

It is a pleasure to announce the formation of the Swiss Society of Allergy (Schweizerische Allergie-Gesellschaft / Société Suisse d'Allergie). A founder's group of forty-six met on July 16 at Berne, adopted the proposed by-laws, and decided to hold the first annual meeting February 25 and 26, 1950, at Zurich. Officers of the Society, which now has 150 members, are as follows: President, Prof. Dr. A. S. Grumbach; Secretary, P.D. Dr. H. Storck; Treasurer, Prof. Dr. W. Jadassohn; 1st Assessor, Prof. Dr. W. C. Loeffler; 2nd Assessor, Prof. Dr. K. Bucher. This first assembly unanimously accepted the formal invitation of the Executive Committee of the International Association of Allergists to become an official member. This is the sixteenth of the existing twenty-four national allergy societies to become an official member of the International Association of Allergists.

The American College of Allergists extends greetings and sincere congratulations on the organization of this Swiss Society of Allergy which has some of the most outstanding scientists of international reputation in Switzerland as its officers.

AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its sixth annual meeting at the Biltmore Hotel, Los Angeles, California, March 6, 7, and 8, 1950. All members of the College who are members of the Academy are urged to attend this meeting which promises to be one of its best. If you are not a member of the Academy, please write to the Biltmore Hotel for a hotel reservation card. If you plan to attend, it would be appreciated if you would notify the Executive Headquarters of the American Academy of Allergy, 208 E. Wisconsin Avenue, Milwaukee 2, Wisconsin.

OMAHA MID-WEST CLINICAL SOCIETY

The Omaha Mid-West Clinical Society held its seventeenth annual clinical assembly October 24 to 28, 1949, at the Hotel Paxton, Omaha, Nebraska. The Society is limited in membership to 155 Omaha physicians who are on the teaching staff of either Creighton University or the University of Nebraska College of Medicine. Its purpose is to offer postgraduate courses for practicing physicians in the midwestern territory. A panel discussion on allergy was presented on Friday, October 28. Dr. J. Harvey Black of Dallas, Texas, Dr. Theodore L. Squier of Milwaukee, Wisconsin, and Dr. Fred W. Wittich of Minneapolis, Minnesota, were guest speakers at this panel discussion.

THE PITTSBURGH ALLERGY SOCIETY

The fall program of The Pittsburgh Allergy Society opened with a meeting on September 19, 1949, at the Women's Hospital, Pittsburgh, Pennsylvania. The guest speaker was Dr. John Mitchell of Columbus, Ohio, who discussed the following subject: Psychogenic Influences in Allergy. There was a large attendance which included representatives from hospital social service departments.

* * *

ANNALS OF ALLERGY, 7:155-300 (March-April) 1949, was indexed under Current Medical Literature of the JAMA 141:153 (September 10) 1949 issue. The article by Rapaport and Peshkin, "Immunity to Diphtheria Induced by Booster Dose of Alcohol-Refined, Alum-Precipitated Toxoids: Based on Study of Fifty-Nine Allergic Children", and "Oral Pollen Absorption: Demonstrated by Controlled Passive Transfer Tests" by Feinblatt and Love were abstracted.

* * *

Dr. Leon Unger has returned from a trip to Great Britain and Ireland. While there, he addressed the British Medical Association at Harrogate on "Nasal Allergy"; the British Association of Allergists at Cardiff, Wales, and the Institute of Microbiology in London on the subject of "Bronchial Asthma"; and the Association of Hospitals in Oxford on the subject of "Migraine".

* * *

Dr. Herbert J. Rinkel, Kansas City, Missouri, a member of the Board of Regents of the College, presented a talk before the Polyclinic of the Hospital for Sick Children in Paris on the morning of June 30. This was by invitation of Professor Robert Debre, Professor of the Medical Clinic for Children. A lecture was also given before the service of the Hospital Staff, Interns and Medical Service of Doctor Lamay, on July 2.

* * *

Allergists who are consulted by surgeons for skin irritations caused by wearing rubber gloves will be interested to know that the B. F. Goodrich Company of Akron, Ohio, after an extensive investigation, has created a glove which when worn by a number of those who had been sufferers from dermatitis has relieved the skin irritation, according to their personal reports. These gloves are now on the market as "Special Purpose" surgeons' gloves.

* * *

Appointment of R. J. Buckman, M.D., to the medical staff of the sales and promotion division of Parke, Davis & Company, Detroit, Michigan, has been announced by H. J. Loynd, Vice President of the Company in charge of Sales and Promotion.

* * *

Albert V. Stoesser, M.D., F.A.C.A., announces the association of Lloyd S. Nelson, M.D., in the practice of allergy and diseases of children at 1409 Willow Street, Minneapolis, Minnesota.

BOOK REVIEWS

THE MICROSCOPE. Its Theory and Applications. By J. H. Wredden, F.R.M.S., Bedford, with a Historical Introduction by W. E. Watson-Baker, A.Inst.P., F.L.S., F.R.M.A., and a Foreword by R. K. Fleming. 296 pages, 298 illustrations. Price, $5.50. New York: Grune & Stratton, 1948.

This most interesting, profusely illustrated book on the use of The Microscope should be read by every physician who uses this instrument. All allergists can profit very much from the information presented herein.

The excellently illustrated Historical Introduction presenting the discovery and development of the lenses up to the devolpment of the compact microscope is worth the price of the book alone.

Apparently, the object of the author was not only to provide general information about the theory and construction of the microscope, but, as he states, "also to set down a number of more unorthodox applications and processes which I have developed as a result of constant use of the instrument."

There is probably no instrument in science today with such an expanding popularity as The Microscope. The author dwells in great detail on the underlying theoretical principles governing the functioning and mechanical construction of the instrument Although the book is primarily intended for those who are studying Microscopy for the first time, it is also designed for those who have had previous experience with the capabilities of the instrument and who wish to make a serious study of it.

The first two chapters are devoted to optical principles which are presented in an attractive and easily understood manner with diagrammatic illustrations. The instrument is then comprehensively treated part by part in succeeding chapters, with discussions in detail of the functions of the eyepiece, objective, condenser, stand, et cetera. Standard applications of the instrument are dealt with by the author who believes that if the basic principles are easily grasped at the outset, then future work with the instrument, when applying optical principles to any particular problem, will be a real pleasure and open up numerous avenues of information.

The author succeeded very well in covering a very wide field within the scope of one volume on The Microscope in a manner which is simple but yet should be of great interest to those interested in newer methods and processes.

The advantages of binocular microscopes are presented in detail as well as the use of the microscope in photography. The final chapters present the use of the microtome, embedding methods, mounting, et cetera.

The Appendix presents various tables of "Refractive Indices of Various Substances," the "Index of Visibility," and "Dispersions of Glasses," as well as equivalent tables for various measures, constants useful to the microscopist, conversion tables of microns to fractions of an inch, and charts on logarithms and anti-logarithms.

The photographs throughout the book are excellent and really works of art.

PROGRESS IN ALLERGY, VOL. II. Edited by Paul Kallós, M.D., Helsingborg, Sweden. 356 pages, 50 illustrations, 37 tables. Price $7.50. Basel: S. Karger, Publisher, 1949. Interscience Publishers, Inc., New York, Agent for the Western Hemisphere. The contributors to Volume II are: Harold A. Abramson, New York; K. Bucher, Basel; Robert A. Cooke, New York; French K. Hansel, St. Louis; Holger Haxthausen, Copenhagen; Elvin A. Kabat, New York; L. Kallós-Deffner, Helsingborg; Foster Kennedy, New York; Hjalmer Koch, Stockholm; Rolf Meier, Basel; Frank A. Simon, Louisville; Lewis Stevenson, New York; George L. Waldbott, Detroit; and Fred W. Wittich, Minneapolis.

The first volume of "Progress in the Science of Allergy—Fortschritte der Allergielehre" appeared before the outbreak of World War II. It is now out of print and because of many popular demands, Volume II has made its appearance. In the present volume, the author recognizes the rapid development in the field of allergy and its theoretical and practical importance. In this volume, as in the former, the principle of publishing "individual contributions covering some special domains in research or clinic" has been adhered to. In an effort to give equal emphasis to theoretical and practical problems, Doctor Kallós devoted a larger part of both of these volumes to pathology, pharmacology and immunology in the broadest sense. The present volume reflects the development in the whole field of allergy in representing various unhindered opinions. There is an excellent introduction by the editor, correlating observations of the various editors. Throughout the book, authors were selected who were pioneers in their field.

The chapter on "Immunochemistry" by Kabat is one of the most concise and complete reviews of immunochemical investigations including the more recently developed quantitative procedures. His chapter alone has 341 references.

The chapter by Wittich on "Allergic Diseases in Animals" has fifty-five references. This chapter offers the first convincing proof of spontaneous allergy (atopy) in the lower animal manifested by typical seasonal hay fever in a dog established by skin tests, passive transfers, to a dog of a different species and to the human skin, positive nasal and ophthalmic tests, as well as successful hyposensitization and the demonstration of thermostable antibodies by means of the passive transfer and precipitin method.

The reactions and results of bronchoscopic therapy in asthma is fully presented by Waldbott. He also has a very practical chapter on "An Etiological Survey of Chronic Urticaria."

There is a chapter beautifully illustrated on "Present Status of Aerosol Therapy of the Lungs and Bronchi" by Abramson, who, during World War II, pioneered in the field of aerosol stabilization and therapy. When an officer on the staff of the Technical Division, Office of the Chief, Chemical Warfare Service, Lt. Col. H. A. Abramson directed the first investigation on the study of penicillin aerosols in animals and man with a view to utilizing this technique in the treatment of lung infections of all types. This investigation was carried on at Cold Spring Harbor. The work of this author formed the groundwork structure from which our present-day knowledge of aerosol therapy stems. The chapter is complete in details and contains seventy-four references.

There are two chapters by Hansel. He places cytological studies of nasal secretions on a practical basis in the chapter on "The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses." He also has a chapter on the use of "Small Dosage Dust and Pollen Therapy." To review this book without describing some of these authoritative chapters in detail would be unfair.

Professor H. Koch of Stockholm has a chapter on "Allergy in the Middle Ear" which is complete and authoritative. The most interesting syndrome complexes are now recognized as being due to hypersensitiveness. Professor Koch has a more elaborate presentation on the subject in *Acta Oto-laryngologica,* from the Otolaryngologic Clinic in Lund.

Professor Holger Haxthausen of Copenhagen presents the most recent observations on the striking allergic skin lesions—urticaria, atopic dermatitis, and the allergic eczemas of the contact type. The author has also presented his observations on allergic phenomena, his own observations on various diseases of the skin which he finds to be of topical interest and classifies some of the manifestations of allergy. The bibliography is most complete.

Frank Simon has a chapter on "Allergy to Human Dander in Infantile Eczema."

Foster Kennedy writes in his characteristic inimitable style on "Allergy of the

Nervous System with Especial Reference to Migraine." There is an Addendum to this chapter by Robert Cooke on "The Basis for Allergy in Diseases of the Nervous System."

A brief chapter on "Allergy as a Cause or a Mechanism in Disseminated Sclerosis" by Stevenson is most opportune.

Von R. Meier and K. Bucher present a complete chapter in German on the pharmacology of the antihistaminics which includes grouping of the various formulas showing their relationship and a comparison of their clinical reactions. With the exhaustless literature written on this subject, it is refreshing to absorb so much valuable information on the antihistaminic antagonists presented so simply in one chapter. There are 187 references.

Finally, the editor and Liselotte Kallós-Deffner have a most complete chapter in German on the clinical use of the histamine antagonists. This includes a report on the influence of Antistine on the histamine skin reactions and the clinical results of the use of this antihistaminic on allergic diseases, particularly acute and chronic urticaria and those urticarias resulting from thermo reactions, angioneurotic edema, neurodermatitis, serum sickness, insect bites, the itching dermatoses, Ménière's disease, histamine headaches, migraine, experimental headaches, allergic nonseasonal rhinitis, hay fever, bronchial asthma, diagnostic skin examinations and histamine antagonists, side effects, with a summary of clinical results obtained in the various allergic diseases with the use of Antistine. This chapter is an example of the thoroughness by which a review should be made and is refreshing when compared with some of the fragmentary reports on some of the antihistaminics which now appear in the literature. In fact, the whole text is characterized by a thoroughness of observations on the subject that is most refreshing.

The publishers are to be congratulated on the paper stock and the illustrations. All physicians in allergy could read this second volume to advantage.

ALLERGY IN RELATION TO OTOLARYNGOLOGY. By French K. Hansel, M.D. 77 pages. 6 colored plates. 2 tables. Price $2.50. Saint Paul: Bruce Publishing Co., 1949.

This small compact volume, an official publication of The American College of Allergists, represents a panel discussion on allergy in relation to otolaryngology which was presented at the Fourth Annual Meeting of The American College of Allergists. Dr. French Hansel, chairman of the panel, presents the opening article detailing succinctly the various procedures necessary for the diagnosing of allergy as encountered by the otolaryngologist. This includes symptomatology, rhinoscopic examination, cytology of the secretions, x-ray examination, bacteriology, pathology, general clinical history, examination and laboratory findings.

There are six colored plates illustrating various grades of eosinophilia as well as a table interpreting the cytologic picture, representing combined allergy and infection.

There is a panel discussion by authoritative allergists who present the various phases of diagnosis and treatment including a discussion of psychosomatic influences.

The book is completed with a section on questions and answers following the panel discussion. There is an excellent reference list.

This is the first compilation on the subject of allergy in relation to otolaryngology and emphasizes the necessity of a close cooperation between the otolaryngologist and the allergist when insuring adequate treatment to the patient. All students of otolaryngology or physicians treating ear, nose and throat diseases can read this little book with profit when applying allergy to their specialty.

Important Announcement

The QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY, the first comprehensive review of allergy and applied immunology, is now published under the auspices of the American College of Allergists. The June and September issues will appear under one cover and launches the *Review* under a new owner and publisher.

The Editorial Board has been completely reorganized Outstanding allergists and immunologists in various parts of the world are on the Contributing Editorial staff, thus making the *Review* international in scope.

Arrangements have been made to have the details of printing the publication handled by the Bruce Publishing Company of Saint Paul, publishers of ANNALS OF ALLERGY.

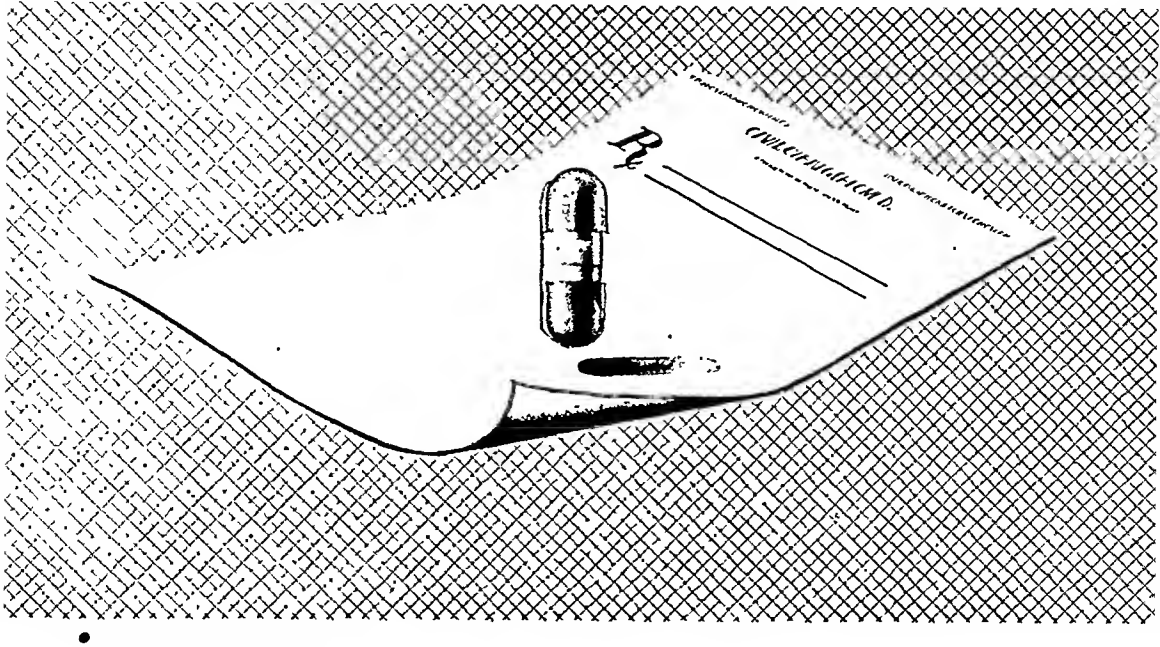
Every effort will be made to embrace in the *Review* the highest grade literature on allergy and applied immunology. Instead of mere abstracts, there will be concise, critical accounts of the publications reviewed. Authors are invited to review their own articles.

Classification of subject matter has been greatly simplified. At the end of each year there will be a title and author index which will represent selected reviews on every phase of allergy appearing in the world's literature.

The *Reviews* will be greatly enlarged. The domestic subscription rate for those who are now subscribers to ANNALS OF ALLERGY will be $5 per year and the rate for non-subscribers to the ANNALS will be $6 per year. Foreign postage will be $1.50 additional. Prepaid subscriptions now in effect will be honored at the rate and on basis paid. The subscription rate is so reasonable that no physician applying allergy to his practice can afford to be without the QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY.

FRED W. WITTICH, M.D.
Editor and Publisher

All orders for subscriptions or renewals should be addressed to the *Quarterly Review of Allergy and Applied Immunology*, in care of the Publication Office, 2642 University Avenue, Saint Paul 4, Minnesota.



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1. Horton, B.T., Ryan, R. E. & Reynolds, J. L., Proc. Staff Meet. Mayo Clinic, 23 105, Mar. 3, 1948.
2. Friedman, A. P., N. Y. State Jl of Med. (in press).
3. Ryan, R E., Postgraduate Medicine (in press).
4. Hansel, F. K , Annals of Allergy (in press).

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1. Brewster, J. M., U. S. Naval Med. Bull. 49: 1-11, January-February 1949.

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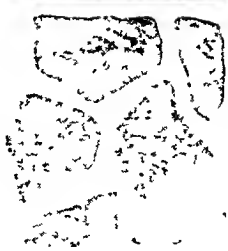

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Rosen, F. L.: J. M. Soc. New Jersey 45: 390 (1948).

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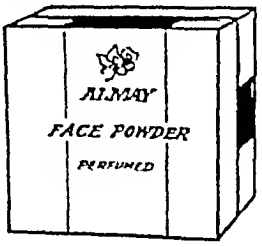

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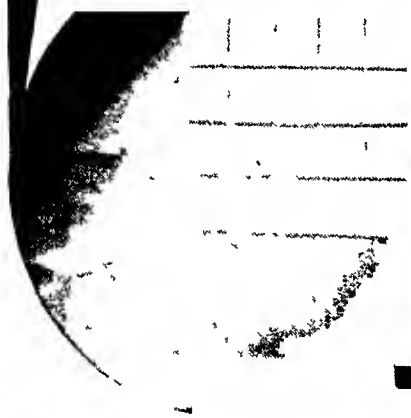

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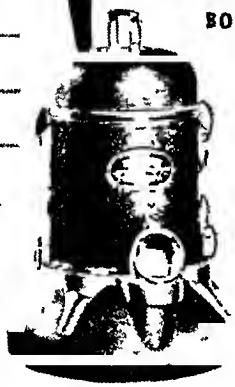

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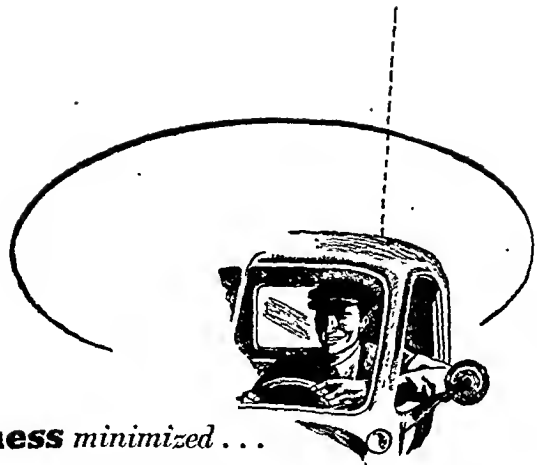

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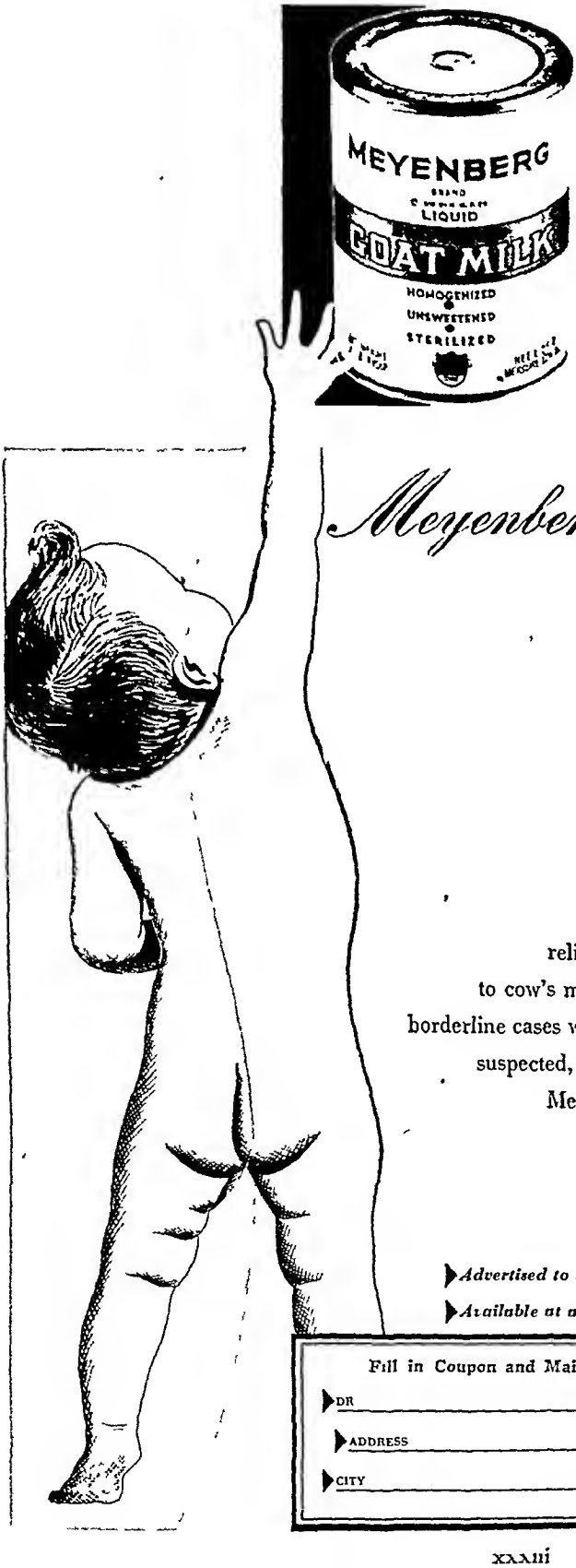

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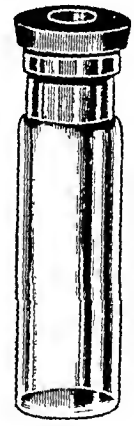

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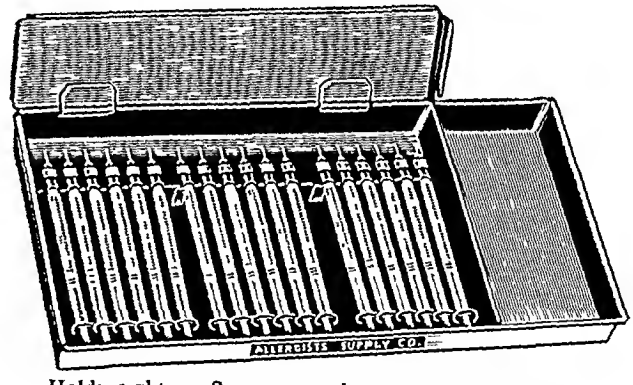

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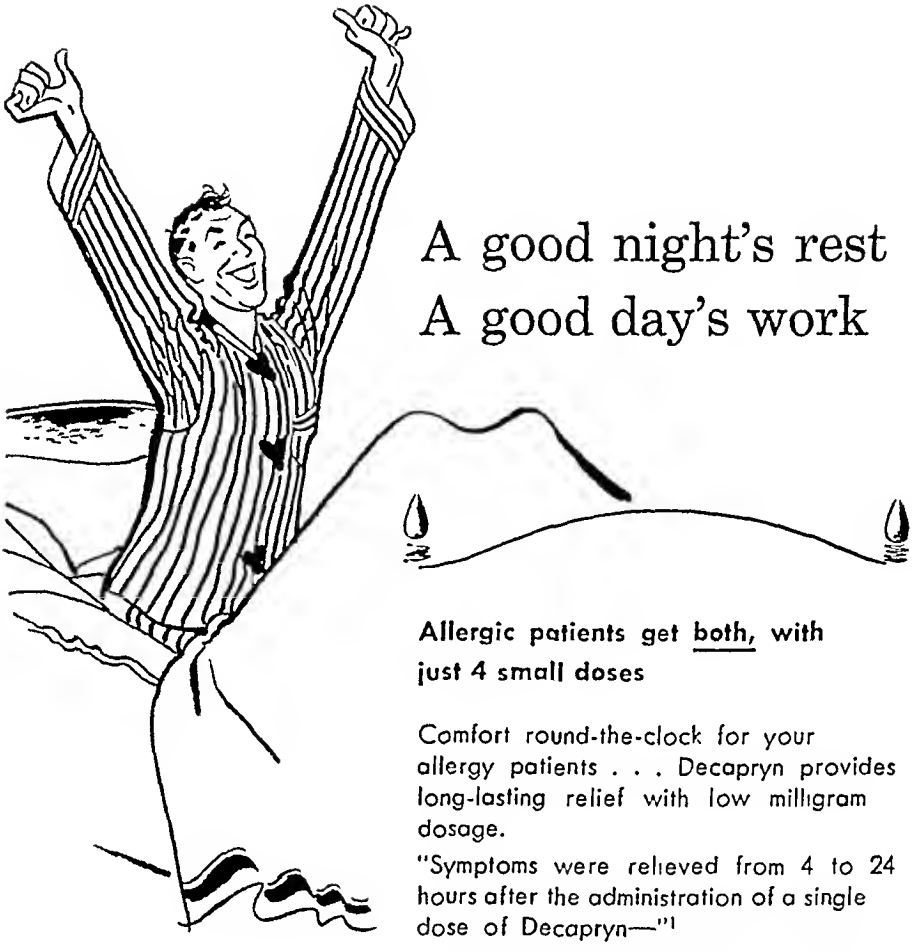

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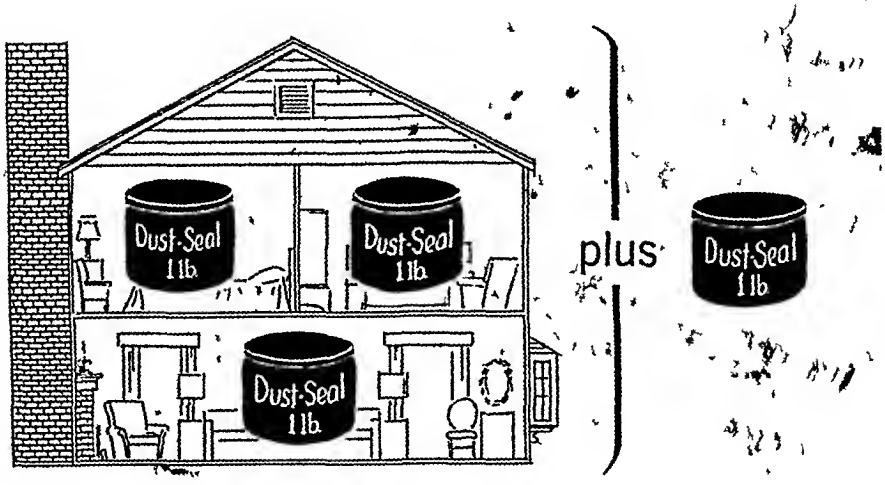

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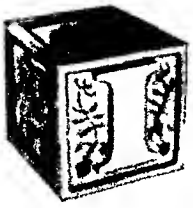

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1 Jones B B: Virginia Med Monthly 74.241 June 1947
2. Levine S Z J A M A., 128.283, May 26 1945
3 Schroeder, L. J et al J Nutrition 32 413, Oct 1946

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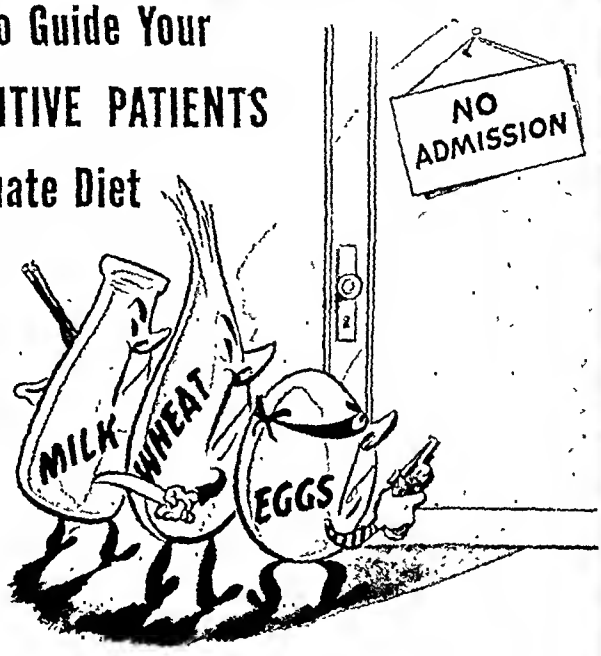

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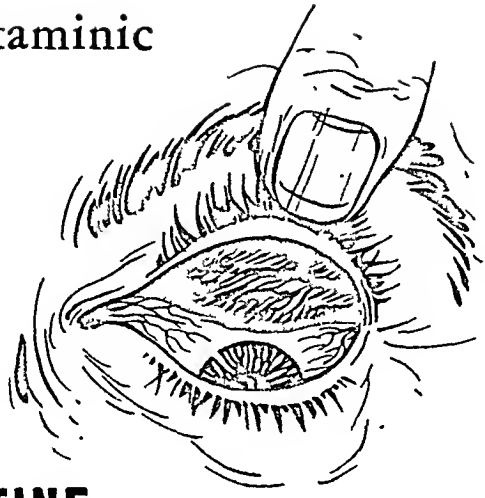

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1. Friedlaender, A. S., and Friedlaender, S.: Annals of Allergy, 6: 23-29, Jan Feb, 1948.

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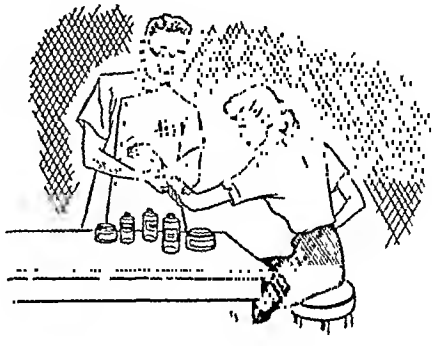

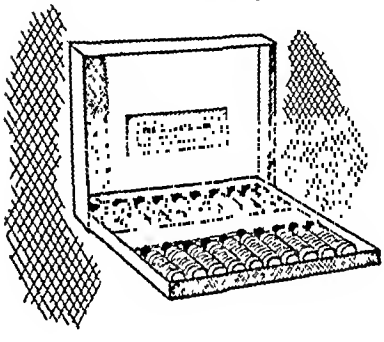

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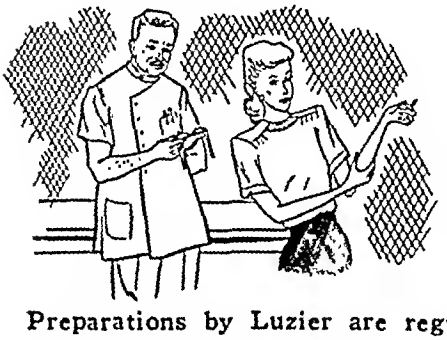

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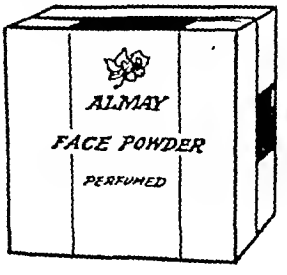

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1. Sheldon, J. M. et al. Univ. Mich. Hosp. Bull. 14.13-15 (1948). 2. MacQuiddy, E. L.: Neb. State M. J. 34.123 (1949)

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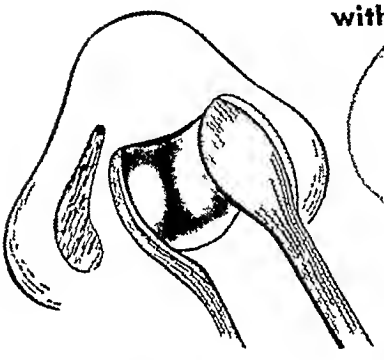

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URTICARIA PHOTOGENICA

Report of Two Cases, One of Them Associated with Purpura Photogenica

STEPHAN EPSTEIN, M.D., F.A.C.A.
Marshfield, Wisconsin

URTICARIA photogenica, also called solar urticaria, is a rare condition. It is characterized by the appearance of erythema and wheals following exposure to natural sun. It may be the only manifestation of the patient's light sensitivity or it may be combined with other lesions, such as eczema solare, prurigo aestivalis. Recently Prieto, Lopez de Azcona and Dochao,[10] Blum, Barksdale and Green,[11] Sulzberger and Baer,[25] Burckhardt,[12] Ehrlich[13] and Beal[5] have reported informative studies of this condition. The following two cases are reported because of the light sensitivity studies carried out and because of the association of a photogenic purpura with one of them.

CASE HISTORIES

Case 1.—Mrs. E. L., a white woman, thirty-four years of age, was seen first on August 1, 1944. She stated that she was "allergic to the sun's rays and to change in temperature." For the past four years, whenever she was exposed to the sun, she began to itch and break out with hives. For four years also she had an eczema on her legs. For the past two months the patient had trouble with menstruation.

General examination did not reveal any significant pathologic changes. Blood count and urinalysis were normal. Scratch and intradermal tests with common antigens were negative or inconclusive.

Her skin was normal except for a typical lichen simplex chronicus behind the left knee and on the left lower leg. Exposure to the sun during the noon hour produced a slight urticaria and redness of the jugular triangle. The face did not break out. The patient was seen during the remainder of the year 1944 and again in 1946. There were remarkable fluctuations of her sunlight sensitivity, which in 1946 was reduced to about one tenth of its former degree.

From the Department of Dermatology, Marshfield Clinic, Marshfield, Wisconsin. Presented at the fifth annual meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

Case 2.—Miss C. L., a white girl, nineteen years of age, consulted us because of urticaria on May 22, 1948. The urticaria originated in January following an attack of influenza and had been present ever since. The patient claimed that she broke out with hives whenever she went outside; it seemed worse when the sun was

Fig 1. *(above)* Urticaria solaris following ten minutes of exposure to natural sun. Wheals are surrounded by erythema. This picture shows the location of the wheal at the site of pressure from the straps of the bra (Case 2).

Fig. 2. Purpura photogenica. Those parts of the feet are spared that were protected from the sun by the straps of the sandals.

shining. The hives lasted from one-half to one hour. Her condition was usually worse during menstruation. The past history was irrelevant, except for an "attack of hives" in 1946, which the patient thought was caused by a woolen skirt. The urticaria left her when this skirt was discarded. Early during the same year, the patient had an attack of pain in her abdomen which was diagnosed clinically as an ovarian retention cyst. The patient felt well in general

TABLE I. LIGHT SOURCES AND FILTERS USED IN DIRECT TESTS AND PASSIVE TRANSFER

No.	Light Source and Filter Used	Shortest Wave Length Transmitted (A)	Case 1 (E. L.)		Case 2 (C. L.)	
			Direct Test	Passive Transfer	Direct Test	Passive Tranfser
1	Natural sun		Pos.	—	Pos.	Pos.
2	Mercury arc lamp "Burdick" unfiltered		Pos.	Pos.	—	—
3	Mercury arc lamp "Kromayer type"					
a	Unfiltered		Pos.	Pos.	Pos.	Pos.
b	Corning filter 791	2200	—	—	Pos.	—
c	Corning filter 986	2600	—	—	Pos.	—
d	Corning filter 597	3100	Pos.	Pos.	Pos.	Pos.
e	Corning filter 738	3400	Pos.	—	Pos.	—
f	Corning filter 511	3500	Neg.	—	Neg.	—

General examination did not reveal any particular abnormalities except for definitely infected tonsils. There were no abscessed teeth. Blood count and urinalysis were essentially normal. Her menstruation was regular but associated with much pain and cramps. Skin tests, scratch tests and intradermal tests with routine allergens were all negative. However, there were rather severe delayed reactions to several bacterial antigens, especially staphylococcic immunogen, streptococcic vaccine, streptococcic immunogen and Friedlander bacillus. When the patient first came to the clinic, no pathologic changes were seen on the skin. However, after she was exposed to the sun for ten minutes, she returned with erythema on the exposed parts and also on that part of the upper body which was covered only by a rather thin blouse. There was no redness underneath the brassiere. However, wheals were formed exactly at the covered places where there was pressure, such as from the straps of the brassiere (Fig. 1). The lower arms and face, although exposed to the sun, did not break out with hives.

Course of Condition.—On June 3, 1948, the patient developed a sore throat. Two days later a purpuric eruption appeared on both lower legs which consisted of hemorrhagic, partially urticarial, irregularly shaped patches. This purpuric eruption of the feet and lower legs was definitely located at the sites exposed to the sunlight (Fig. 2). The areas covered by the various buckles and strips of leather which formed the front part of the shoe were free. The patient was hospitalized between June 7 and 11. She improved rapidly following treatment with penicillin. Two weeks later, the tonsils were removed. Culture from the tonsils yielded pneumococci and streptococci.

On July 4, the patient noticed a new, though milder, purpuric eruption of both lower legs. It was preceded for an hour by an urticarial eruption. Small purpuric lesions appeared on top of them. Since then there has been no further purpura.

The patient was treated with antihistaminics, niacin amide, and creams containing tannic acid, and para-aminobenzoic acid. The sun sensitivity showed great fluctuations. She is able to tolerate sunlight better now but is not free from the solar urticaria.*

STUDIES OF LIGHT SENSITIVITY

Determination of Active Wave Length.—To determine approximately the responsible wave lengths in these two cases, various light sources and filters were used as shown in Table I.

*This patient was presented at the meeting of the Minnesota Dermatological Society in Marshfield, Wisconsin, September 18, 1948. The proceedings of this meeting will be published in the *Archives of Dermatology and Syphilology.*

These tests indicated that the same spectral regions were active in both cases. Exposures to one second of unfiltered ultraviolet were sufficient to elicit the response at a time of high sensitivity, whereas the 597 filtered light required at least 30 seconds under similar circumstances. These ex-

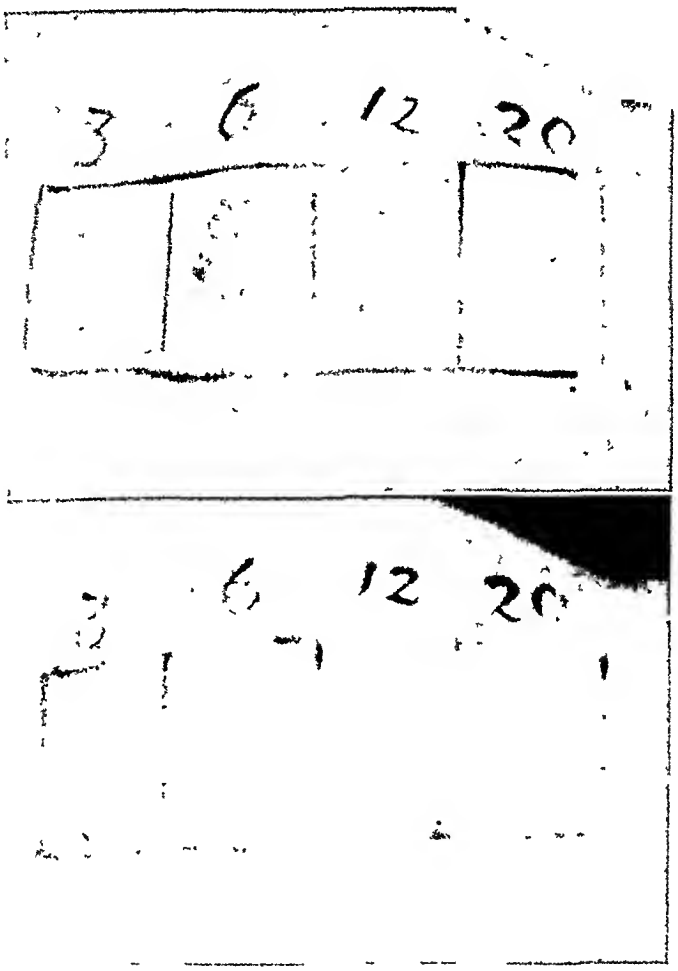

Fig. 3. Wheals caused by sunburn rays. Four fields were exposed to unfiltered mercury arc light (Kromayer lamp) for three, six, twelve and twenty seconds respectively. Upper picture shows immediate wheaing response which parallels the delayed sunburn reaction twenty-four hours later, shown below.

periments indicated that several spectral regions, sunburn spectrum and longer ultraviolet might be responsible in our cases. The wheals, as is well known, are always confined to the irradiated site; there are no pseudopods. However, the wheal is slightly larger than the irradiated field. The wheals produced by the long ultraviolet alone subsided faster than those elicited by unfiltered ultraviolet. The dependence of the wheaing reaction on the sunburn rays is shown in Figure 3. This applies only to short exposures where the influence of the longer wave lengths probably can be neglected.

The role of the longer ultraviolet, between 3,100 and 3,400 Å, was

TABLE II. PREVENTION OF EXPERIMENTAL URTICARIA SOLARIS BY PARA-AMINO-BENZOIC ACID (PABA)
Applied as 15% ointment in Ruggle's cream or in Eucerin

Light Source	Skin Protected by PABA Ointment			
	Direct Test on Patients		Passive Transfer Test	
Kromayer lamp	Immediate Reaction Wheal	Delayed Reaction Sunburn	Immediate Reaction Wheal	Delayed Reaction Sunburn
(1) Unfiltered Light Containing Sunburn Rays				
Short Exposure	0	0	0	0
Medium and Long Exposure	+	0	0	0
(2) Filtered Light (Corning 597) No Sunburn Rays (3100 A)				
Short Exposure	+ but somewhat diminished reaction		0	
Longer Exposure	+		0	

demonstrated by the fact that filtered light (Table I, 3d) which did not allow sunburn radiation to pass, readily produced whealing.

Whether there existed also sensitivity beyond this spectral region seems rather doubtful. The significance of positive passive transfer through the light of a fluorescent lamp is not clear. Two sites produced a wheal after forty minutes exposure at 25 cm. distance, whereas a third site, previously successfully challenged with 597 filtered light, did not respond. Direct tests with this lamp on the patient were negative, but they were performed at a period of low sensitivity. While the energy levels of this lamp below 3,600 Å are near zero, there is probably also some output at 3,100 Å and 3,400 Å.

Filter tests can provide only approximative information. As monochromatic light was not available, studies were performed concerning the protective action of para-aminobenzoic acid (PABA) incorporated into ointments.

Protective Action of Para-aminobenzoic acid (PABA) in Urticaria Photogenica.—Beal's[5] patients were not protected from solar urticaria by PABA. Its protective action was studied in both our cases in regard to direct tests and, in Case 1, also in passive transfer tests. The results are summarized in Table II.

Direct tests: With short exposures of three to five seconds, PABA ointment prevented the urticarial wheal. With longer exposures, PABA cream did not prevent the wheal, although the sunburn rays were filtered out by it. This is shown in Figure 4. These tests demonstrated again that ultraviolet longer than the sunburn spectrum was also a factor in our cases.

The wheal produced by longer ultraviolet (Corning filter 597) was not prevented by the PABA ointment although it was slightly diminished with short exposures. This can be easily explained by comparing the action

spectra of sunburn and urticaria solaris with the absorption spectrum of PABA (Fig. 5). The latter shows great absorption within the range of the sunburn rays, but far less in the longer ultraviolet.

In passive transfer tests, however, PABA ointment prevented whealing

Fig. 4. Para aminobenzoic acid (PABA) and urticaria photogenica. The upper half of the two fields is protected by PABA ointment. This ointment does not prevent the wheal following longer exposure to unfiltered mercury arc lamp *(above)*, although the ointment protected against the sunburn reaction *(below)*

from a good sunburn dosis (Fig. 6) and also from longer ultraviolet (Corning filter 597).

I am not able to explain this paradoxical behavior; however, in the passive transfer experiment the PABA ointment had been rubbed into the skin for a longer time, which may account for the greater protective action in these tests.

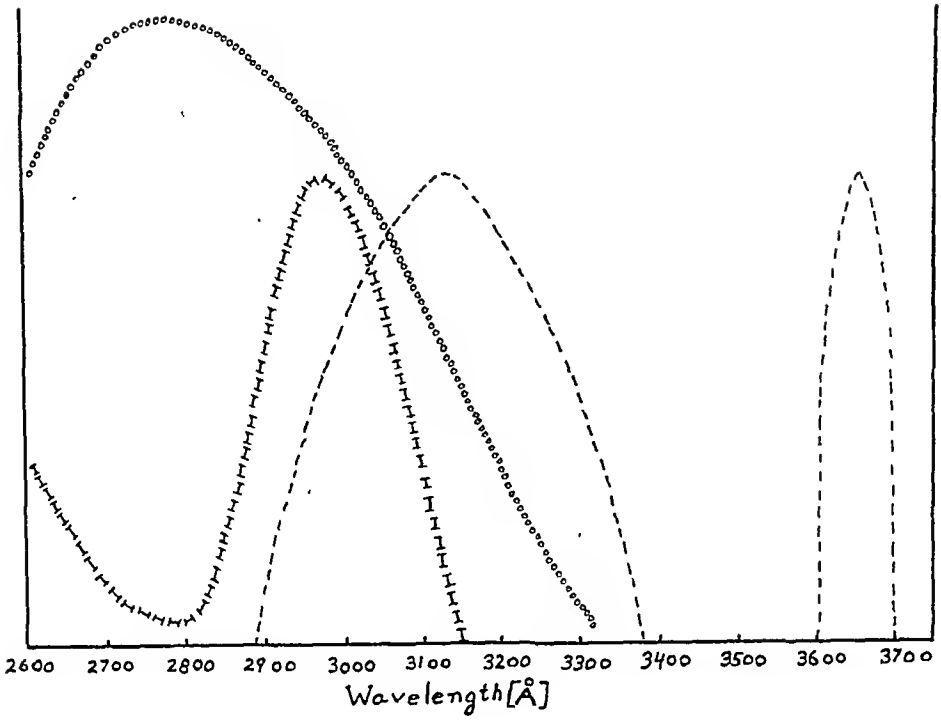

Fig. 5.

Sunburn spectrum of normal skin
Sensitivity spectrum in urticaria solaris
Absorption spectrum of para-aminobenzoic acid
(Schematic after Blum, Burckhardt, Beal, Rothman)

Further Observations.—Our patient in Case 1, besides the urticarial reaction, also presented repeatedly a delayed sunburn-like reaction to long ultraviolet (Kromayer lamp light through filter 597). About two hours after an irradiation of twenty-two minutes an erythema with follicular swelling appeared. It was still present after six hours (Fig. 7) but gone after twenty-four hours. It was not followed by pigmentation. The appearance of the erythema, with its follicular location, its course and the lack of pigmentation, distinguishes this reaction from a sunburn erythema. A similar pathologic reaction to probably the same spectral region had been reported previously by Epstein.[15]

The following observation indicates specific changes in local sensitivity. A site that had reacted to unfiltered ultraviolet was retested two months later with filtered light (Corning filter 597). The old field was still marked by mild pigmentation. This second test was carried out also on the surrounding area. The urticarial wheal appeared first at the site of the previous test, and was decidedly more marked there.

Purpuric lesions never appeared with the urticarial reaction. In one test, only one of many, two purpuric spots appeared with the sunburn reaction.

Action of Antihistaminics.—Pyribenzamine, 100 mg., given over a period of one to one and one-half hours prior to the light sensitivity tests, reduced the response at a time of high sensitivity. Such an influence was not noted when the patient's sensitivity was low.

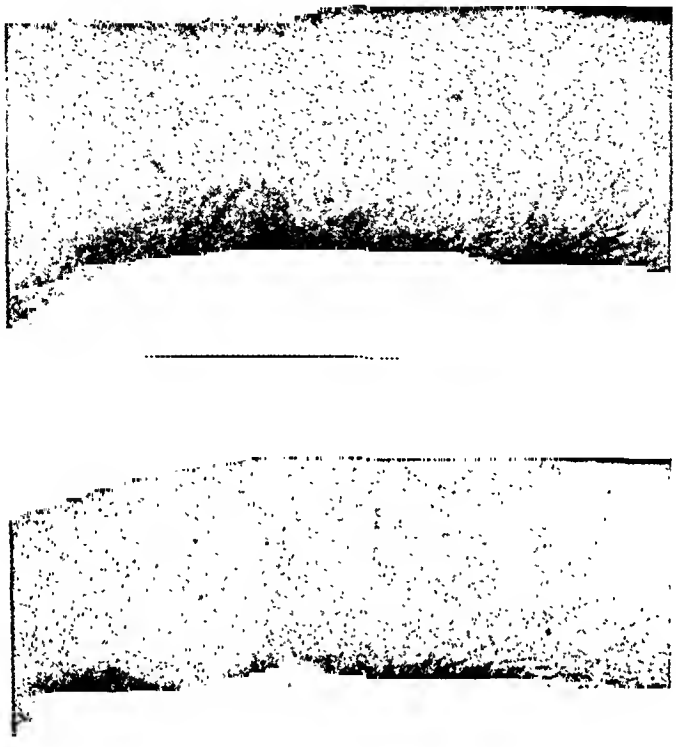

Fig. 6. Prevention of passive transfer reaction from unfiltered ultraviolet through PABA ointment. Serum from the patient was injected in two sites. The left side was protected by PABA ointment. Following irradiation, there was an immediate positive passive transfer reaction only at non-protected site at right *(above)*. The lower picture shows the sunburn reaction. No reaction occurred at the site at the left protected by PABA.

Prolonged oral administration of Pyribenzamine and Histadyl reduced the natural sensitivity. Experimentally it could be demonstrated that the sensitivity had been reduced to about one-fifth to one-tenth of the previous level. These changes in sensitivity may not have been due solely to the antihistaminics; natural variations and the influence of other therapeutic measures, such as niacin amide, have to be considered. But discontinuation of the antihistaminics usually was followed by increased sensitivity.

Passive Transfer.—Passive transfer by means of the Prausnitz-Küstner test was repeatedly positive in both cases; 0.2 to 0.3 c.c. of serum were used for each test. Our observations are in agreement with the findings of others (Rajka,[20] Sulzberger and Baer,[25] Ehrlich,[13] Beal[5]).

1. Passive transfer was always positive on several test persons at times of high sensitivity on the part of the patient. When her sensitivity was light, passive transfer was usually negative.

2. Serum is more potent when taken after irradiation of the patient.

Fig. 7. Delayed inflammatory reaction to exposure to longer ultraviolet (Kromayer lamp through Corning filter 597, twenty-two minutes). Erythema, especially around follicles, was noted after two to six hours; it was gone after twenty-four hours, no pigmentation. No reaction occurred in several normal controls following the same exposure.

This had been found by Rajka and shown especially well by Beal.

3. Passive transfer could not be carried out with serum inactivated for two hours at 55° Centigrade.

4. Previous irradiation of the serum with unfiltered ultraviolet light, with a dose several times an erythema dose, did not affect noticeably the passive transfer test. Such a procedure inactivated the serum in Beal's case and produced a considerably smaller wheal in Rajka's experience. This difference of the findings may be due to a different antibody titer of the sera tested and also a varying length of irradiation.

5. Passive transfer was elicited by the same wave length which was active on the patient.

6. Sites of passive transfer challenged successfully with unfiltered ultraviolet light did not react to later challenges with filtered long wave ultraviolet, and vice versa.

7. Passive transfer "in reverse," i.e. irradiation of the donor's skin prior to the injection of the serum, also was positive.

Passive Transfer in Reverse.—In these experiments the skin was first irradiated and the serum was injected subsequently. These experiments are presented in Table III.

Filtered light was used which would not produce a sunburn erythema so as not to interfere with the observation. Controls were carried out

TABLE III. PASSIVE TRANSFER IN REVERSE

Experiment I	1. Preparation of Donor	2. Serum Injected 5-10 Minutes after Irradiation	3. Immediate Reaction	4. Subsequent Challenge Irradiation 24 Hours Later
Serum				
Case I	Skin irradiated	0.3 cc.	Negative	Negative
Normal (control)	Skin irradiated	0.3 cc.	Negative	Negative
Case I (control)	Skin not irradiated	0.3 cc.	Negative	Urticarial reaction
Experiment II		10-30 Minutes after Irradiation		
Serum				
Case I	Skin irradiated	0.3 cc.	Erythema + increasing wheal after 15-60 minutes.	Negative
Normal (control)	Skin irradiated	0.3 cc.	Negative	Negative
Case I (control)	Skin not irradiated	0.3 cc.	Negative	Urticarial reaction
Experiment III		10-15 Minutes after Irradiation		
Serum				
Case I	Skin irradiated	0.3 cc.	Doubtful reaction	Slight reaction, much less than control
Normal (control)	Skin irradiated	0.3 cc.	Negative	Negative
Case I (control)	Skin not irradiated	0.3 cc.	Negative	Urticarial reaction

with normal serum injected into irradiated skin as well as with the patient's serum in normal skin. These tests are complicated by the fact that the injection of 0.2 to 0.3 c.c. of serum always produces a wheal which lasts from one-half to two hours. In some experiments, the test seemed negative, as had been Rajka's experience; there was no difference of the wheals between the serum which had been injected into irradiated skin and the wheal produced in normal skin. In other experiments there was a more or less outspoken whealing reaction with erythema which could be distinguished from the normal wheal due to the serum alone. On the following day the sites so treated were irradiated again. Then, with one single exception, the sites where the patient's serum had been injected into previously irradiated skin, did not show any reaction whatsoever, regardless whether there had been a *clinical* reaction on the original test or not. But on all previously not irradiated sites, a triple response developed. (Fig. 8.)

These experiments indicate that an antigen-antibody reaction had taken place in this passive transfer in reverse. This is quite evident for those instances where this reaction was manifested clinically. But there seems also to be a satisfactory explanation for the "negative" reactions. It apparently takes some time after the injection of the serum before a passive transfer test appears positive. According to Rajka, irradiation during the first hour after the injection was negative, whereas this negative phase in Beal's case was less than thirty minutes. Neither of these authors, however, reports whether these sites reacted to subsequent irradiation. In one case (Table III, third experiment) a slight reaction occurred also

after twenty-four hours. Apparently the previous early reaction had not exhausted all antibodies. That a subsequent challenge may be positive under such circumstances in the regular passive transfer had been reported by Baer.[1]

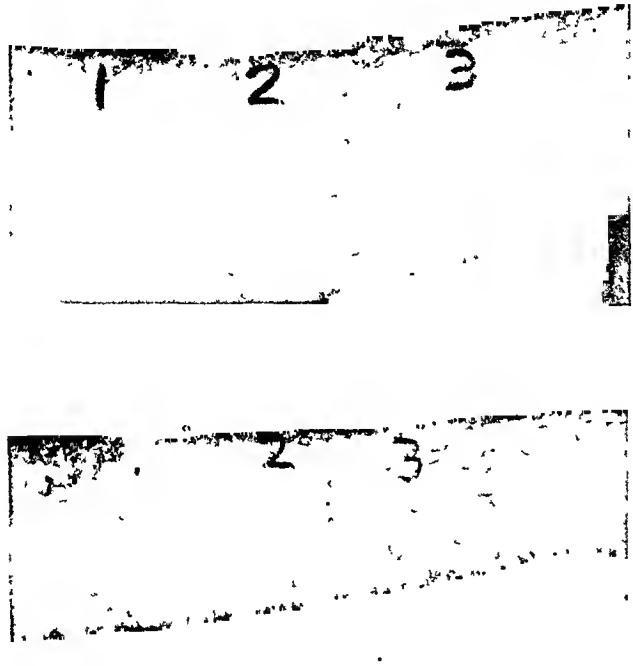

Fig. 8. Passive transfer "in reverse" (Table IV). *(Above)* Positive passive transfer in reverse at site 1. This area had been irradiated first, and then the patient's serum was injected. No reaction occurred at controls 2 and 3. At site 2, serum from a normal person was injected following irradiation. Also no reaction occurred at site 3, where the patient's serum had been injected into non irradiated skin. *(Below)* Result of rechallenge after twenty-four hours. All three sites were exposed to filtered ultraviolet light. Immediate wheaking response occurred only at control site 3; there was none at site 1, where passive transfer in reverse had been positive the day before.

DISCUSSION AND COMMENTS

Mechanism of Urticaria Photogenica.—The mechanism of solar urticaria has been clarified largely by the careful and excellent studies of Blum and of Rothman and their co-workers.[5,8,9,10,11,22] Two types of urticaria solaris are distinguished in principle, as seen in Table IV:

1. Urticaria solaris caused by visible light. Here the violet and blue light of a wave length of 4,000 to 5,000 Å has been found active. This seems to be the rarer type. Passive transfer has been negative in the three cases reported.

2. Urticaria solaris caused by ultraviolet. This type had been originally designated by Blum, Baer and Sulzberger[10] as urticaria solare $<$ 3,700 Å. In general these patients are sensitive to the sunburn spectrum and longer

TABLE IV. URTICARIA SOLARIS (U. S.)

Type	Sex	Active Wave Length in Å	Passive Transfer
I. U. S. Caused by Visible Light			
Violet and Blue Light			
Arnold [3]	Male	4,000-5,000	Negative
Blum, Allington and West [9]	Male	4,000-5,000	Negative
Blum, Barksdale and Green [11]	Male	4,000-5,000	Negative
II. U. S. Caused by Ultraviolet			
(a) $\lambda < 3700$			
Abramson [1]	Female	< 3,700?	—
Burckhardt [12]	Male	2,900-3,700	Positive
Sulzberger and Baer [25]	Male	2,500-3,700?	Positive
Ehrlich [13]	Female	3,000-3,700?	Positive
(b) $\lambda < 3400$			
Beal[5] Case I	Female	2,900-3,400?	Positive
Case II	Female	2,900-3,150	Positive
Epstein Case I	Female	2,900-3,400?	Positive
Case II	Female	2,900-3,400?	Positive
Prieto, Lopez de Azcona and Dochao [19]	Female	3,000-3,400?	Positive

ultraviolet. However, within this group there are further differences. So far there seem to be two sub-groups. One is sensitive to wave lengths below 3,400 Å; in the other also longer ultraviolet, around 3,650 Å, seems to be effective. All of the older observations are based on studies using light filters. It is known that light filters are a not too reliable method. Their shortcomings have been discussed elsewhere.[15]

Recently Burckhardt[12] and Beal[5] have tested their patients with monochromatic light. Beal's two patients reacted to sunburn rays around 2,900 Å and to the longer ultraviolet of 3,131 Å. Burckhardt's patient, however, in addition to this spectral region, also gave a whealing response to the wave length of 3,650 Å. Beal's experience bears out also the lack of reliability of glass filters. According to the filter tests, one of his patients reacted to irradiation longer than 3,250 Å whereas the experiments with the monochrometer revealed no sensitivity beyond the 3,131 Å line.

From our tests it would seem that our two patients are sensitive to the same spectral region as Beal's, whereas Ehrlich's and Sulzberger and Baer's cases apparently also reacted to 3,650 Å.

The passive transfer tests in all patients sensitive to ultraviolet were positive regardless of the difference of their spectral range. As patients with solar urticaria are sensitive to different spectral regions, the question arises whether the same antigen is responsible or whether there is more than one metabolite activated by light. Blum[8] and Beal have searched for and thought of substances with absorption spectra corresponding somewhat to the active wave length of their cases, but actually nothing is known about the antigen as yet. Beal believes that the natural metabolites which are supposed to be formed by a photochemical reaction are different according to the absorption range. Even if there are different metabolites, our experiments with the passive transfer tests indicate that there was only one antibody in our cases. Once the antibody was exhausted by filtered light, no reaction could be elicited by unfiltered light, and vice versa.

Prieto and his collaborators[19] as well as Sulzberger and Baer[25] have suggested that the antigen is produced or released by the action of sunlight on the skin of normal people. Such a background for all physical allergy at first was suggested by J. Jadassohn.[18] Prieto assumes that this substance appears more slowly or in smaller amounts in the skin of normal individuals, because the latent period between irradiation and the appearance of the lesions is greater in the case of the passive transfer than in the direct test on the patient.

It has been noted by several observers that the face and hands, the most exposed parts of the body, are usually less severely involved in urticaria solaris. This is in direct contradistinction to another light sensitivity disease, prurigo aestivalis. In this condition, face and hands are usually most severely afflicted. Considering this different relationship, the observation of desensitization following antihistaminics and other phenomena of local sensitization, it would seem more likely to ascribe this relative freedom of the exposed parts to actual desensitization rather than to increased natural resistance.

Contributing Factors.—Not much is known about precipitating factors. In some instances, overexposure to the sun marks the beginning of the solar urticaria. In our Case 1, the patient dated the onset following an attack of influenza. The relationship of other sun sensitivity diseases with infection is well known. I may mention Sonck's[24] report of numerous cases of prurigo aestivalis in patients with lymphogranuloma inguinale. The role of mechanical stimuli such as pressure in photosensitivity is known (Gottron and Ellinger[17]). The clinical observation in our case 2 demonstrates that pressure was a factor in her solar urticaria. The patient's history related an incident where the wheals were first noted on the part covered by the shoe. Clinical exposure led to an erythema of the uncovered parts, but the wheals appeared first on those parts of the shoulders which were covered by the straps of the brassière. In experimental tests, however, as a rule, wheals could not be produced by pressure only, even if simultaneously lesions of solar urticaria had been produced. There was only one occurrence which suggested possibly the additional role of pressure. In one experiment with filtered light under compression an irregular erythema of equal intensity appeared at the sites irradiated for two, three, and five minutes. There was no wheal and no itching. In another similar experiment, a site treated for three minutes showed the same type of erythema, whereas a site irradiated for five minutes failed to react.

The prevalence of the female sex in urticarial solaris has been noted by Rajka.[20] Adding to his twenty-four cases the twelve cases of urticaria solaris reported later on (Table IV), we find that the ratio of females to males is 26 to 10. It is interesting to note that other light sensitivity diseases also show a predilection for the female sex. That goes for prurigo

aestivalis as well as hydroa vacciniformis. In the latter condition, according to Senear and Finck,[23] the female sex prevails 2 to 1.†

The sex relation has been linked to hormonal factors; ovarian disfunction was indicated in several cases and also in ours.

The association of urticaria solaris with other allergic conditions does not seem very impressive from the literature. Both of our patients have suffered from skin allergies, urticaria in one instance and lichen simplex chronicus in the other; but there was no family history of major allergies, and skin tests also were negative.

The combination of urticaria solaris with purpura in our Case 2 is unique. It seems likely that the solar urticaria served only as a means of localization for the purpuric eruption which otherwise was dependent upon the tonsillar infection. This purpura should not be confused with the condition described as purpura solaris by Berlin.[6,7] Berlin's purpura solaris is a hemorrhagic tendency exhibited in some cases of colloid degeneration of the skin. This condition consists of hemorrhagic spots of different sizes and shapes. The condition is confined to the uncovered parts of the body and occurs always on the dorsa of the hands. Both sexes are involved equally, older people more frequently. The condition disappears spontaneously after five to ten days.

Treatment of Solar Urticaria.—Solar urticaria caused by violet and blue light does not seem amenable to treatment, although spontaneous fluctuations of the sensitivity occur. Solar urticaria due to ultraviolet light apparently can be helped more or less by antihistaminics.** Treatment with antihistaminic drugs and attempts to eliminate precipitating factors seem at present the best therapeutic chance. Protective creams which prevent sunburn are not effective, unless they absorb also the longer ultraviolet rays.

SUMMARY

Two cases of urticaria photogenica are reported, one complicated by purpura. Both patients were sensitive to the rays of the sunburn spectrum and to longer ultraviolet. Passive transfer tests were positive in both instances.

Experimental studies of the light sensitivity in these cases, with a discussion of recently reported cases, are presented.

REFERENCES

1. Abramson, H.: Proc. Soc. Exper. Biol. & Med., 43:410, 1940.
2. Abramson, Harold A.: Psychosom. Med., 10:114-117, 1948.
3. Arnold, H.: Arch. Dermat. & Syph., 43:607-620, 1941.

†It may be just a coincidence that three cases of proven sensitivity to violet and blue light (Table IV) all occurred in males. But one may mention in this connection that in hydroa vacciniformis, notwithstanding the preponderance of the female sex in general, there is a rare hereditary form where the male sex is afflicted nearly exclusively.

**For review about the protection afforded by antihistaminic drugs and other drugs against sun sensitivity, the reader is referred to a recent review by the author (16).

4. Baer, Rudolph L.: Discussion on Beal.[5] J. Invest. Dermat., 11:433, 1948.
5. Beal, Peter L.: J. Invest. Dermat., 11:415-433, 1948.
6. Berlin, Ch.: Acta dermat.-venereol., 20:77, 1939.
7. Berlin, Ch.: Brit. J. Dermat., 58:274-279, 1946.
8. Blum, H.: Photodynamic Action and Diseases Caused by Light. New York: Reinhold Publishing Company, 1941.
9. Blum, H.: Allington, H., and West, R.: J. Clin. Investigation, 14:435, 1935.
10. Blum, H.; Baer, R., and Sulzberger, M. B.: J. Invest. Dermat., 7:99, 1946.
11. Blum, H.; Barksdale, E., and Green, H.: J. Invest. Dermat., 7:109, 1946.
12. Burckhardt, W.: Dermatologica, 94:202-206, 1947.
13. Ehrlich, E. E.: Ann. Allergy, 5:478-487, 1947.
14. Epstein, Stephan: J. Invest. Dermat., 5:225-241, 1942.
15. Epstein, Stephan: Arch. f. Dermat, u. Syph., 168:67-87, 1933.
16. Epstein, Stephan: Ann. Allergy, 6:617-623, 1948.
17. Gottron, H., and Ellinger, F.: Arch. f. Dermat. u. Syph., 164:11, 1931.
18. Jadassohn, J.: Die Toxicodermien. Die Deutsche Klinik am Eingange des zwanzigsten Jahrhunderts. Dermatologie. Vol. 10, No. 2, pp. 117-153 and 119-120. Berlin-Wien: Urban und Schwarzenberg, 1905.
19. Prieto, Lopez de Azcona and Dochao: Arch. f. Dermat. u. Syph., 183:287-296, 1942.
20. Rajka, E.: J. Allergy, 13:327-345, 1942.
21. Rothman, Stephen, and Henningsen, A. B.: J. Invest. Dermat., 9:307-313, 1947.
22. Rubin, Louis; Beal, Peter L., and Rothman, Stephen: J. Invest. Dermat., 8:189, 1947.
23. Senear, F. E., and Fink, H. W.: Arch. Dermat. & Syph., 7:145, 1923.
24. Sonck, C. E.: Acta dermat.-venereol., 20:529, 1939.
25. Sulzberger, M. B., and Baer, R.: J. Invest. Dermat., 6:345, 1945.

IMPORTANT NOTICE

It is realized that because the date of the sixth annual convention of the College has been advanced two months, the time for preparation of papers to be presented at the St. Louis meeting in January is relatively short. As announced in the editorial in this issue, there will be two simultaneous programs. Thus, every member has an opportunity to present material. This is in accordance with the liberal attitude of the College towards its members. New members are joining the College daily; some of these men have sufficient material to present a short thesis of such quality as to qualify them for Active Fellowship, and they should be afforded this opportunity.

The aim of the Program Committee is twofold: First, to arrange these papers in an effort to satisfy the majority of those members who have a broad view of the scope and functions of the College; i.e., to direct their interests so that they may become efficient allergists. Second, to give every opportunity to specialists in allergy to present results of fundamental observations of an investigative nature.

The time is short, so please submit your manuscript with an abstract to the Chairman of the Program Committee, Dr. Sim Hulsey, 701 Fifth Avenue, Fort Worth, Texas, as soon as possible. The deadline for papers, in order to be announced in the program, is November 15. There will be a full quota of technical exhibits. There is also excellent booth space on the Mezzanine floor of the New Hotel Jefferson for scientific exhibits. We urge members to present scientific exhibits which are so essential to the success of an annual meeting.

THE CLINICAL APPLICATION OF A NEW PIPERAZINE COMPOUND

I. Human Pharmacology

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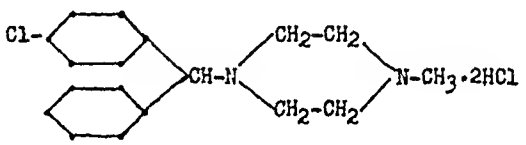
IT is the purpose of this communication to present the results of pharmacological studies which have been carried out in humans with a new antihistaminic compound[1,4] of chemical structure distinctly different from the usual ethylenediamine types which are now available. This compound is N-methyl-N'-(4-Chlorobenzhydryl) piperazine dihydrochloride†, (Compound 47-282), for which we have recently adopted the name of "Perazil" Chlorcyclizine.

Compound No. 47-282



Pharmacological studies in animals[10] reveal that Compound 47-282 has marked activity against the spasmogenic action to histamine on the excised guinea pig trachea[7,8,9] and on the ileum. To a lesser degree, it inhibits the contractions produced by acetylcholine and barium. When given orally, in relatively small doses, this drug prevents or reduces for over twenty-four hours the severity of bronchoconstriction following exposure of guinea pigs to an atmosphere of nebulized histamine. Antianaphylactic activity is exhibited by this compound when given orally to guinea pigs sensitized to horse serum or egg white. Circulatory studies in dogs show that the depressor effects of histamine and acetylcholine are inhibited by the intravenous administration of 47-282 and that the pressor effect of epinephrine is enhanced. No deleterious effects on the heart or respiration are seen. Acute toxicity in mice and chronic toxicity in rats and dogs indicate that this drug is relatively nontoxic.

A series of pharmacological studies were carried out with Compound 47-282 in a group of human volunteers. These studies comprised: (1) inhibition of histamine wheal-response, (2) incidence of toxic side effects, and (3) circulatory effects.

From The Wellcome Research Laboratories, Burroughs Wellcome and Co. (U.S.A.) Inc., Tuckahoe, N. Y.

Presented at fifth annual meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

†It has recently come to our attention that this compound in the form of the monohydrochloride has been synthesized and investigated independently with substantially the same results by the Abbott Laboratories, North Chicago, Illinois.

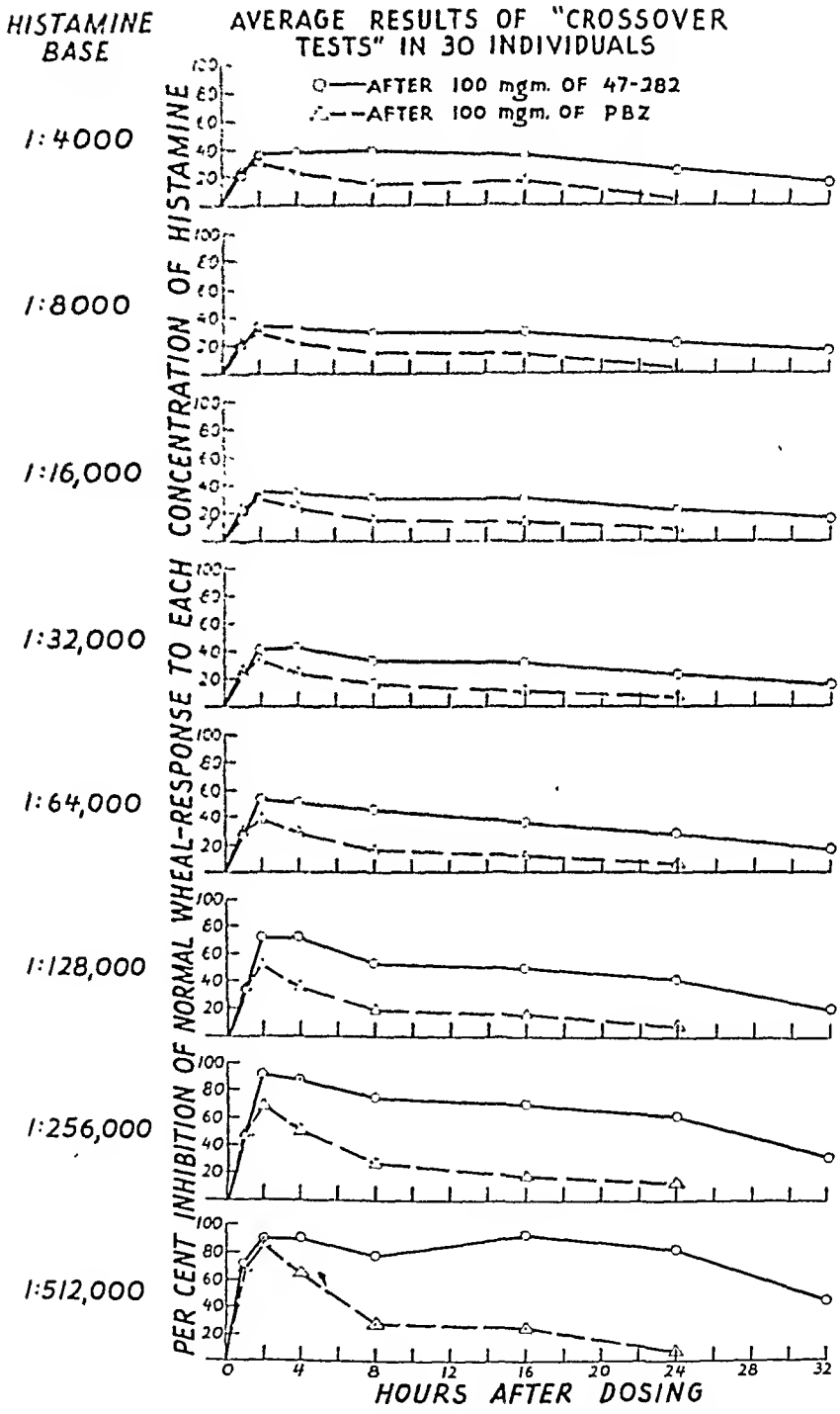


Fig. 1. Inhibition of wheal-response to histamine in humans after the oral administration of Compound 47-282 and Pyribenzamine.

INHIBITION OF HISTAMINE WHEAL RESPONSE

Experimental—In order to estimate the relative activity of Compound 47-282, it was compared with a popular antihistaminic (Pyribenzamine) as a standard. Tests were made of the comparative abilities of the two

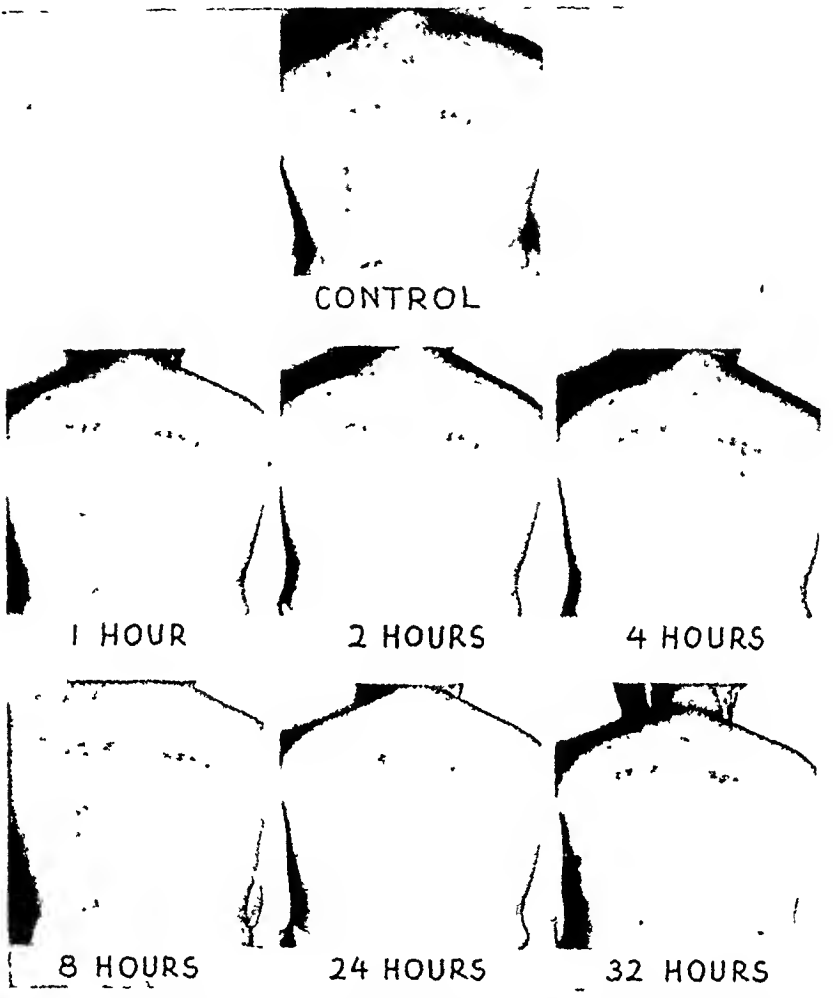


Fig. 2 Patient N A—inhibition of whealing Patient was given 100 mg Compound 47 282 orally after control reading made Note duration of effect

drugs to inhibit the action of histamine in producing wheals on the human skin. In carrying out the experiment, a "cross-over" design was used, in which each drug was tested in turn on the same individual. Available for these tests was a group of thirty white subjects—fifteen females and fifteen males; ages from twenty to forty-seven years—of whom sixteen were allergic and fourteen nonallergic In order to compensate for possible "carry-over" effects, half of the group received Compound 47-282 first and half Pyribenzamine. After a suitable recovery period, the subjects were again tested. Those who had first received 47-282 now received the standard, and those who had received the standard now received 47-282.

Each subject was treated as follows: Eight uniform circular scratches

were made in a vertical row on the subject's back with a long hollow trocar about 1 mm. in diameter. (A similar instrument can be made from an Edwards Bleeding Needle, 14 gauge.* The instrument was held perpendicular to the skin and rotated with only sufficient pressure to scarify the

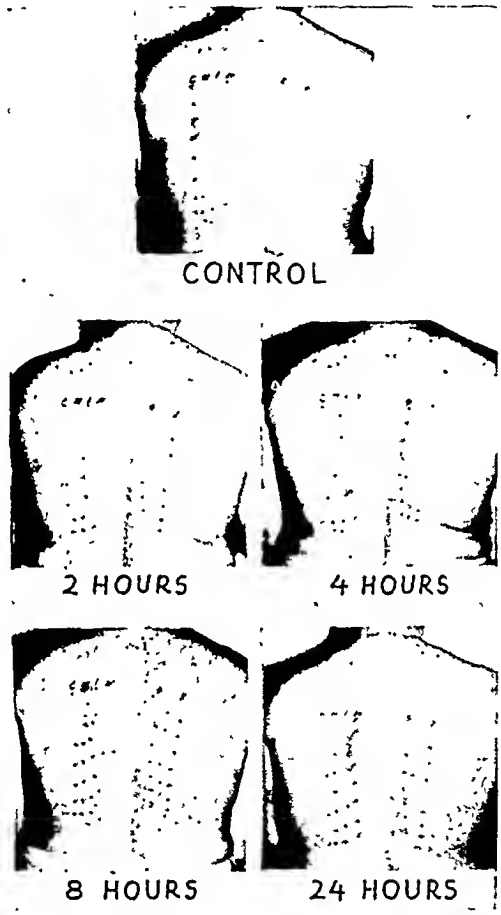


Fig. 3. Patient N. A.—inhibition of whealing. Patient was given 100 mg. Pyribenzamine orally after control reading made. Note duration of effect.

epidermal layer of the skin, care being taken not to cause bleeding. One of eight histamine solutions was applied to each scratch, allowed to act for ten minutes and then wiped dry. The solutions were prepared by two fold dilution, starting with 1 :4,000 and ending with 1 :512,000 of histamine base. The diameter of each resulting wheal was measured. These values were recorded as controls. One hundred milligrams of the antihistamine drug was then taken orally. At the end of one hour a new row of wheals was produced and measured. This procedure was repeated at two, four, eight, sixteen, twenty-four, and thirty-two hours after dosing. All scratches and measurements were made by the same person (S.H.J.).

*Obtained from the Haver-Glover Laboratories, Kansas City, Missouri.

TABLE I. CROSS-OVER TEST. HISTAMINE CONCENTRATION = 1:256,000. TIME = 4 HOURS. WHEAL DIAMETERS IN MM.

Group A				Group B			
Subject	First 47-282	Second Pbz	Diff.	Subject	First Pbz	Second 47-282	Diff.
Kwed.	0.0	1.0	—1.0	Ide	0.5	0.0	0.5
Burg.	0.0	1.0	—1.0	Lôrz	2.5	0.0	2.5
Carn.	0.0	1.0	—1.0	Torn.	1.0	2.0	—1.0
Duff.	0.0	1.5	—1.5	Pac.	2.0	0.0	2.0
McCa.	0.0	1.0	—1.0	Mur.	1.5	0.0	1.5
Gall.	0.0	1.0	—1.0	Cast.	2.0	1.0	1.0
Rhd.	0.0	1.0	—1.0	Coll.	1.5	0.0	1.5
deB.	0.0	1.5	—1.5	Nug.	1.0	0.0	1.0
Grah.	0.0	1.5	—1.5	Hear.	1 0	0.0	1.0
Ligh.	0.0	1.5	—1.5	Whel.	0.0	0.0	0.0
diG. M.	0.0	0.0	0.0	Bonn.	2.5	0.0	2.5
Lang	0.0	1.0	—1.0	deG. J.	2.5	0.5	2.0
Cngm.	0.0	0.0	0.0	Weis.	0.0	0 0	0.0
Wnuck	2.0	2.0	0.0	And.	0.0	0.0	0.0
Dost.	1.0	1.0	0.0	Dews	1.5	1.5	0.0
Sd			—13.0				14.5
$\bar{d}$			— 0.87				1.12
Sd^2			16.00				29 25
$(Sd)^2/N$			11.27				14.02
$S(d-\bar{d})^2$			4.73				15.23

$$s = \sqrt{\frac{4.73 + 15.23}{15-1 + 15-1}} = 0.844$$

$$t = \frac{1.12 - (0.87)}{s\sqrt{\frac{1}{15} + \frac{1}{15}}} = 6.46$$

This value for t corresponds to a probability of more than 0.001 and is highly significant.

Results.—Approximately 3,800 measurements were recorded. The resulting data are analyzed graphically in Figure 1, where results are expressed as a per cent of the pretreatment or control wheal and plotted against time. Each point represents thirty observations.

It will be observed that 47-282 produced a greater degree of inhibition and that the effects lasted much longer (thirty-two hours) than those produced by Pyribenzamine (Figs. 2 and 3). This is particularly obvious with the more dilute histamine solutions which serve to discriminate more sharply between the two drugs.

In order to determine if the effects produced by 47-282 really were significantly larger than those produced by the standard, statistical analyses were made by calculating *t* values according to the procedure described by Brandt.[5] A typical calculation is illustrated in Table I. For the 1:256,000 dilution of histamine at the four-hour period, *t* was found to be 6.46; at the twenty-four-hour period it was 8.13. Both of these values are highly significant and correspond to probabilities greater than 0.001. This means that Compound 47-282 was beyond question longer in action than Pyribenzamine.

The "cross-over" design is quite efficient and compensates for many variables which may be beyond the experimenter's control. Some of these

TABLE II. INCIDENCE OF TOXIC SIDE EFFECTS. COMPARISON OF 47-282 AND PYRIBENZAMINE WHEN GIVEN ORALLY IN DOSES OF 100 MG.

Drug	Number of Subjects	Total Number of Doses	Individual Doses Producing Side Effects			
			Drowsiness Only		Drowsiness and Other Symptoms	
			No.	%	No.	%
47-282	30*	63	17	26.9	21	33 3
PBZ	30*	56	24	42.8	33	58 9

*Same group of individuals.

may be more important than others. In these experiments, for instance, the difference in the response of individuals to the control application of the 1:256,000 histamine solution was not significantly greater than the difference within the individual. An analysis of variance gave a variance ratio, F, of 1.267, which is somewhat below the customary level of significance. It is not unreasonable to expect that more data would establish such significance. It seems unlikely that the difference in the order of dosing was of much importance. This leaves the difference in drug action as the major factor in the "cross-over" test which, of course, accounts for the significant difference obtained by the test.

Since it has been suggested that the amount of antigen influences wheal size, tests were made on nineteen subjects by applying variable amounts of a solution of histamine to scarified skin areas. Results indicate that the size of the wheal is not influenced by the volume applied.

INCIDENCE OF TOXIC SIDE EFFECTS

During the course of the "cross-over" test the incidence of side reactions was recorded. These complaints, together with those obtained in additional experiments carried out in the same individuals, are summarized in Table II.

It will be observed that of sixty-three individual oral doses of 100 mg. of Compound 47-282 given to thirty subjects, seventeen (26.9 per cent) caused some degree of drowsiness, and a total of twenty-one (33.3 per cent) produced drowsiness and other symptoms. In the case of Pyribenzamine, of fifty-six doses, twenty-four (42.8 per cent) caused drowsiness, and a total of thirty-three (58.9 per cent) produced drowsiness and other symptoms.

The "other symptoms" referred to in Table II are, in the order of their higher incidence, as follows: dryness of mouth, nausea, headache, light headedness, nervousness, difficulty in walking, vomiting, vertigo, palpitation, inability to concentrate, stimulation, and tingling of the fingers. With Compound 47-282 the most common complaint was that of drowsiness; however, it was of mild degree compared to that produced by Pyribenzamine.

CIRCULATORY EFFECTS

Three subjects, with three typical ranges of blood pressure, each took orally 400 mg. of Compound 47-282 in one dose. Systolic and diastolic pressures were recorded at various intervals during a period of seven hours. As shown in Figure 3, no significant changes were observed. It is interesting to note that none of these three subjects experienced any toxic effects.

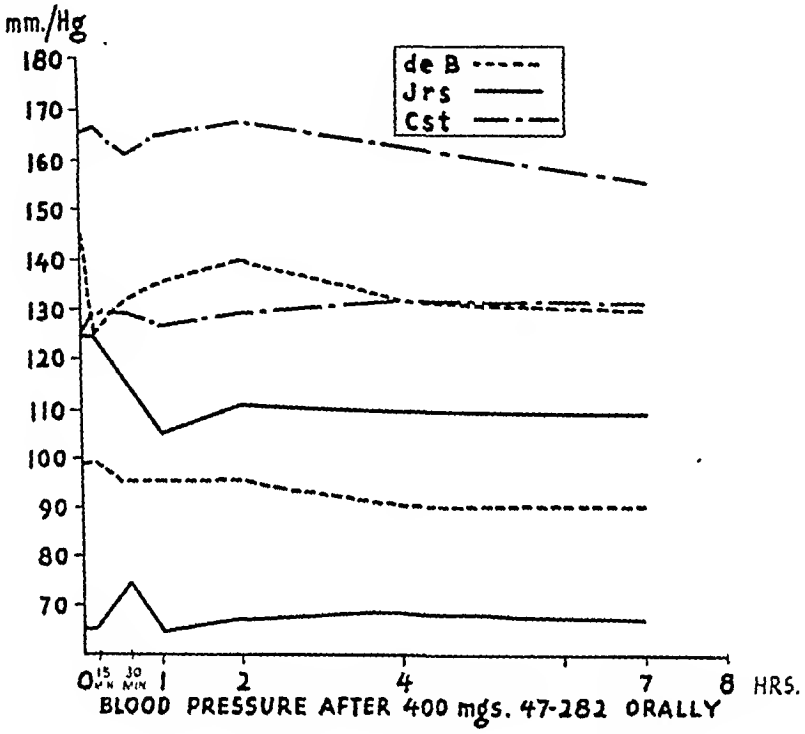


Fig. 4. Blood pressure after 400 mg. of 47-282 orally.

DISCUSSION

In producing the histamine reaction in the skin of humans, some investigators[2,6,11,15,16] use the intradermal injection, others prefer the scratch method, and recently the iontophoretic technique has been introduced. In the experiments presented in this paper, the scratch method was chosen because it is simpler to carry out and is of less discomfort to the subject. Slight modifications were made of the methods previously described.[11,15] All tests were made within a limited skin area of the back in order to minimize errors due to variations with different anatomical locations.

Of the "triple response" resulting from the application of histamine to the abraded skin, it was decided to measure only the size of the wheal, since it has been reported by numerous investigators[2,3,6,13,16,18] that the size of the wheal is a more reliable index of the reactivity of a subject. It has been noted by the same and other workers[17] that the flare is rather nonspecific and could be due, in part, to injury to the skin.

In spite of the many antihistaminics which are now available to the clinician, the search for the ideal antihistaminic continues unabated. Dale[11] has recently encouraged further this quest. The criteria for the ideal antihistaminic are suggested in an editorial which appears in a recent issue of the J.A.M.A.[12] In that article it is recommended that any new antihistaminic drug which is presented to the Council of Pharmacy and Chemistry for acceptance should offer at least one of the following advantages over the agents already accepted: (1) a greatly increased potency over those now available, (2) much less toxicity than those now available, (3) a much greater duration of action, preferably for twenty-four hours, and (4) other than antihistaminic action which may interfere with the allergic mechanism. It is felt that in presenting Compound 47-282, most of these criteria are met.

SUMMARY

Pharmacological studies in humans with N-methyl-N'-(4-Chlorobenzhydryl) piperazine dihydrochloride (Compound 47-282), "Perazil" brand Chlorcyclizine, a new antihistaminic, revealed the following:

1. A marked ability to inhibit the histamine wheal response.
2. A single oral dose imparted definite protection for over twenty-four hours.
3. A very low incidence of toxic side effects.
4. Massive single oral doses fail to elicit any deleterious effect on the circulation.

The authors wish to express their grateful appreciation for the co-operation exhibited by the volunteers who subjected themselves to the human pharmacology and toxicity study.

REFERENCES

1. Albro, L. P.; Baltzly, R., and Phillips, A. P.: Unsymmetrically disubstituted piperazines. II. Histamine antagonists. J. Organic Chem., (In press).
2. Bain, W. A.; Hellier, F. F., and Warin, R. P.: Some aspects of the action of histamine antagonists. Lancet, 255:964, (Dec. 18) 1948.
3. Baer, R. L., and Sulzberger, M. B.: Effect of Pyribenzamine on dermographism. J. Invest. Dermat., 7:201, 1946.
4. Baltzly, R.; Dubreuil, S.; Ide, W. S., and Lorz, E.: Unsymmetrically disubstituted piperazines. III. N-methyl-N'-Benzhydryl piperazines as histamine antagonists. J. Organic Chem., (In press).
5. Brandt, A. E.: Research Bulletin 234, Agricultural Experimental Station, Ames, Iowa.
6. Brown, B. B., and Warner, H. W.: The pharmocologic properties of 2-[α-(2-dimethylaminoethoxy)-α-methyl benzyl]-pyridine succinate, a new antihistaminic agent. J. Lab. & Clin. Med., 33:325, 1948.
7. Castillo, J. C., and de Beer, E. J.: The tracheal chain. I. A preparation for the study of antispasmodics with particular reference to bronchodilator drugs. J. Pharm. & Exper. Therap., 90:104, 1947.
8. Castillo, J. C., and de Beer, E. J.: The excised guinea pig trachea in the study of antihistamine drugs. Fed. Proc., 6:315, 1947.
9. Castillo, J. C., and de Beer, E. J.: The tracheal chain. II. The anaphylactic guinea pig trachea and its response to antihistamine and bronchodilator drugs. J. Pharm. & Exper. Therap., 94:412, 1948.

(Continued on Page 489)

THE CLINICAL APPLICATION OF A NEW PIPERAZINE COMPOUND

II. Clinical Observations

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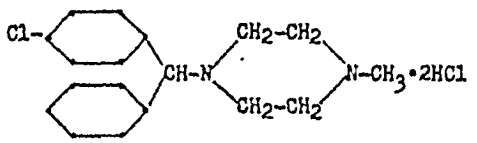
IT has been shown[5] that Compound 47-282, N-methyl-N'-(4-Chlorobenzhydryl) piperazine dihydrochloride, "Perazil" brand Chlorcyclizine, the structural formula of which appears below, has outstanding antihistaminic properties, particularly from the standpoint of intensity and duration of action as determined in animal and human experiments. This new compound is of a chemical structure distinctly different from the usual ethylenediamine type of antihistaminics which are already on the market.

Compound No. 47-282

N-methyl-N'-(4 Chlorobenzhydryl) piperazine dihydrochloride



It is the purpose of this communication to present the results of preliminary clinical trials with this agent in the treatment of various allergic conditions.

MATERIAL AND METHODS

A group of sixty-five white subjects, having a total of eighty-four types of allergic symptoms, are presented. The greater number of symptoms reported treated is due to the fact that a number of patients suffered from two concomitant clinical conditions, such as asthma and pollinosis. All were ambulatory patients seen at the allergy clinic of the St. John's Riverside Hospital, Yonkers, New York, and in private practice. The majority of the subjects previously had used some other antihistaminic, and all objective and subjective comparisons were made on this basis. Observations and opinions as to the relief of the patient were compiled on the basis of notations made independently by several allergists who had seen the subjects in the clinic.

It must be remembered that in this area the pollen counts were higher in September, 1948, than in 1946 and 1947. A large percentage of the patients receiving Compound 47-282 were given other antihistaminics, such as Pyribenzamine, Neohetramine and Thephorin at various intervals, and the patients were allowed to state their preference for the drug in terms of efficacy, duration of action and side effects. The majority

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TABLE I. CLINICAL RESULTS—SYMPTOMATIC RELIEF WITH COMPOUND 47-282, 50 MG. ORALLY ONCE DAILY.

Clinical Disease	Number	Improved				Unimproved		Toxicity	
		Excellent		Moderate					
		No.	%	No.	%	No.	%	No.	%
Hay Fever	23	22	95.7	1	4.3			2	8 7
Urticaria Acute	6	6	100.0						
Chronic	1	1	100.0						
Dermatitis Atopic	8	8	100.0						
Contact	3	3	100.0						
Others	7	6	85.7			1	14 3		
Vaso. Rhinitis	21	18	85.7	2	9.5	1	4 8	2	9 5
Bron. Asthma	13	2	15.4	8	61 3	3	23 3		
Sinusitis	2	2	100.0						
Totals	84	68	81.0	11	13.0	5	6 0	4	4 8

of the patients were receiving concomitant specific hyposensitization. The only subjects in this group that received the compound were those who still had moderate to severe uncontrolled symptoms. In general, more relief was experienced by those who were receiving hyposensitizing injections. It was noticeable, however, that those without treatment, having severe symptoms, were relieved with one dose of 50 mg. of Compound 47-282.

In order to have a more uniform evaluation of clinical results, the dose of Compound 47-282 was maintained at 50 mg., once a day, orally. If the patient complained of symptoms during the night or early morning, the medication was offered before retiring. If the patient complained of severe symptoms during the day, the dose was given in the morning. All of the antihistaminics in this clinical evaluation were given orally in the form of tablets or capsules. All results were noted on a basis of 50 mg. once a day, before changing to another dosage regimen. This was purposely done even though it is acknowledged that the level of tolerance and effective dosage varies from one individual to another.

It is noteworthy that even though the drug is quite bitter, it is well tolerated by adults as well as children. A dose of 25 mg. in children (eight to twelve years old) gave comparable results to 50 mg. in adults. For children the drug was masked with cane sugar or with jams and jellies that the child could tolerate without allergic reaction.

Most subjects were seen at least twice a week, and the remainder, weekly, for a minimum period of one month.

Complete blood counts were made on a group of ten patients who had taken the drug daily, for periods of from one week to one month.

RESULTS

Table I illustrates the clinical categories in which symptomatic relief was obtained for twenty-four hours on a dosage of 50 mg. orally, once a day. Clinical evaluation of relief was simply restricted to whether they

were improved moderately or in an excellent manner. Slight relief was considered equivocal and designated as unimproved.

Hay Fever.—During the ragweed pollen season in the fall of 1948, twenty-three cases of hay fever were treated. Twenty-two (95.7 per cent) had excellent relief, and one (4.3 per cent) had moderate relief. All of the patients in this group were improved. Of this number, only two (8.7 per cent) showed any side effects. In the patient who presented moderate relief there was less sneezing, rhinitis, and pruritus of the eye, ear, nose and throat. In the patients who had excellent relief, all of these symptoms, as well as nasal obstruction, were relieved.

Urticaria.—Seven patients, six with acute urticaria and one of the chronic type, were treated. All seven patients (100 per cent) experienced excellent relief. The pruritus was immediately relieved, with a marked reduction in the whealing seen in the acute cases. In the chronic case the edema subsided less markedly, but the pruritus was immediately improved. No toxicity and no side effects were noted.

Dermatitis.—In this category were seen eight patients having the atopic variety and three of the contact type. All eleven (100 per cent) of the patients experienced excellent relief. Other forms of dermatitis, such as trichophytids, lichen planus and undiagnosed types, comprised seven patients, six of whom (85.7 per cent) experienced excellent relief, and one (14.3 per cent) was unimproved. The complaint of pruritus was immediately relieved, and in some cases of the atopic and contact variety the erythematous lesions began to fade. One case that was unimproved was an allergic eczema of nine months' duration which had a neurodermatitis superimposed. No toxicities were noted.

Vasomotor Rhinitis.—In all these twenty-one patients there was a minimal amount or no superimposed infection. Eighteen (85.7 per cent) showed excellent improvement; two (9.5 per cent) showed moderate improvement; one (4.8 per cent) was unimproved. Most patients noticed a prompt subsidence of nasal congestion so that adequate ventilation was again established. Sneezing and rhinitis subsided. A number of patients remarked about the lessened amount of postnasal drip. Two of the group (9.5 per cent) exhibited toxic side effects.

Bronchial Asthma.—These asthmatic patients were of the perennial type even though a number of them had seasonal hay fever. The observations made on most of these asthmatics were over a period of six months, which included two months of the pollen season. It might be said, generally, that the patients who experienced relief of their asthma could be ascribed to the complete relief of the hay fever symptoms. Of this group, two

(15.4 per cent) had excellent relief; eight (61.3 per cent) had moderate relief; three (23.3 per cent) were unimproved. No toxicities were noted.

Sinusitis.—These patients suffered from perennial hyperplastic sinusitis of the infectious type but at the time of treatment did not have a full-blown superimposed infection, with the exception of a slight coryza. Both these patients (100 per cent) experienced excellent relief, manifested by the cessation of headache, lessened postnasal drip and an apparent abortion of the incipient coryza. No toxicities were observed.

TOXIC SIDE REACTIONS

It is stated again that almost all of these patients had had previous experiences with other antihistaminic drugs. Therefore, it is of significance that there was an over-all improvement, in all clinical categories, of seventy-nine (94 per cent) and only an incidence of four (4.8 per cent) toxic symptoms at the dosage level of 50 mg. orally once a day.

Higher doses were given to the same and other patients on different occasions, to one patient, for example, who was suffering from a severe "serum sickness" type of reaction to penicillin. In order to assure a prompt relief, 100 mg. doses were given every two hours for six doses the first day (600 mg.); 100 mg. every four hours for four doses (400 mg.) for the next three days, and then 50 mg. every four hours (300 mg.) for the next three days. This patient experienced prompt relief of the intense pruritus and gradual subsidence of the joint swellings. No toxic symptoms were reported by the patient even though he had remarked of the severe symptoms he had previously experienced with Pyribenzamine and Benadryl. It is possible that by giving the drug more frequently the intensity and prolongation of effect can be obtained, as has been recently shown[3] with other antihistaminics. Another patient, suffering from a "serum sickness" type of reaction, given six 50 mg. doses over a period of sixteen hours, had marked relief of his complaints. This subject notices also no toxic symptoms, even though he had experienced marked side effects previously with Pyribenzamine and Benadryl.

The safety of Compound 47-282 as to its effect on the circulatory system has already been reported.[6] Ten human subjects taking daily 50 mg. doses of Compound 47-282 orally, for periods of one week to one month, showed no significant changes in hemoglobin concentration, leukocyte and erythrocyte counts and differential count. These findings are in accord with those observed with other antihistaminic drugs.[4,7]

DISCUSSION

Prefacing any further remarks, it should be stated frankly that there was great hesitancy in presenting what might be considered an overly enthusiastic report. It would seem from the review of animal and human pharmacology, as well as the clinical observations, that Compound 47-282 approaches more closely the ideal antihistaminic agent than others now

available, since, in our hands, it is the least toxic and has the longest duration of action. The average incidence of improvement with this compound is 94 per cent. In hay fever and urticaria the results approach 100 per cent. In vasomotor rhinitis, without superimposed infection, a 95 per cent incidence of improvement is seen. In asthma, favorable results were seen in 76 per cent. This latter high figure may be due, in part, to the fact that many of these patients were suffering from pollen asthma during the period of observation. Toxic side effects were seen in only 5 per cent of the patients at a 50 mg. dose level. These side effects, when seen, were very mild. The most prominent symptom is drowsiness. This side effect may be entirely desirable, as pointed out by others,[2,8] in the treatment of the allergic patient since he may tend to be less apprehensive and more relaxed.

When compared to the same categories of allergic diseases the clinical effectiveness of Compound 47-282 seems to be of a higher order than the estimated efficiency[1,5] of the presently available antihistaminic drugs.

This new type of synthetic drug should prove to be a valuable agent in offering symptomatic relief while other measures of allergic management are instituted, such as elimination of specific allergens or hyposensitization.

SUMMARY

1. "Perazil" brand Chlorcyclizine, Compound 47-282, is a very potent antihistaminic agent exhibiting a prolonged activity of twenty-four hours.

2. "Perazil" has relieved an average of 94 per cent of the common allergic symptoms.

3. A very low order of incidence of toxicity is seen with no observed serious side effects.

4. Clinical experiments indicate greater efficiency and less toxicity than with Pyribenzamine.

5. "Perazil," an antihistaminic drug of a new chemical group of compounds, is presented as an adjunct to the basic therapeutic methods in the management of allergic disease.

REFERENCES

1. Arbesman, C. E.: The pharmacology, physiology and clinical evaluation of the new antihistaminic drugs (Pyribenzamine and Benadryl). New York State J. Med., 47:1775, (Aug. 15) 1947.
2. Bernstein, T. B.; Rose, J. M., and Feinberg, S. M.: New antihistaminic drugs (Benadryl, Pyribenzamine and Neo-antergan) in hay fever and other allergic conditions. Illinois M. J., 92:90-95, (Aug.) 1947.
3. Craver, B. N.; Cameron, A., and Youkman, F. F.: Comparative effectiveness of five antihistaminics vs. histamine-induced spasms in canine Thiry-Vella loops. J. Pharm. & Exper. Therap., 93:168, 1948.
4. Criep, L. H., and Aaron, T. H.: Neohetramine, an experimental and clinical evaluation in allergic states. J. Allergy, 19:215, 1948.
5. Feinberg, S. M.: Histamine and antihistamine drugs. J.A.M.A., 132:703, 1946.
6. Jaros, S. H.; Castillo, J. C., and de Beer, E. J.: The clinical application of a new piperazine compound. I. Human pharmacology. Ann. Allergy, 6:458-465, (July-Aug.) 1949.
7. Peirce, J. D., and Mothersill, M. H.: Treatment of allergic symptoms with a new antihistaminic drug. J. Indiana M. A., 40:739, 1947.
8. Waldbott, G. L.: The antihistaminic drugs. J.A.M.A., 135:207, 1947.

ANTIGEN-ANTIBODY MECHANISMS IN NEUROTROPIC VIRUS DISEASES

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THE introduction of a morphological approach to the problems of antigen-antibody reactions has added to the armamentarium by which these difficult questions must be answered. Medical history shows adequately the incisiveness of the microscopist's attack. The methods of immunology, pathology, and the clinique are augmented and helped by the recent advances in our knowledge by which allergic mechanisms may be deduced from the dynamics of the cellular pathology of diseased organs. This knowledge has but recently been entered into the literature, and a detailed review is possible.

The plasma cell is the key to allergic processes. Since its description by Cajal[7] (as the cianophil cell) in 1890, it has attracted the attention of many observers, and a voluminous literature, mostly speculative, was accumulated in the four succeeding decades. This older literature has been adequately reviewed by Michels,[22] whose work on the plasma cell in encephalitis will be mentioned later. What may be termed the newer literature on the plasma cell, dealing experimentally with its relation to allergic processes and antibody formation, had its inception in the report of Kolouch[20] in 1938, who described the concomitance of a plasmacytic development in the bone marrow of rabbits with induced hypersensitivity and then alteration of these cells by anaphylactic shock. These observations led to a large series of investigations dealing with the origin of the plasma cell, its significance in antigen-antibody reactions, its chemistry, and its pathological significance. A review by Fagraeus,[11] herself an active contributor to this field, should be consulted for the literature through 1947, as well as the reviews of Kolouch, Good, and Campbell,[21] of Bjorneboe and Gormsen,[2] and of Good.[13] It will be seen that the following facts have been thoroughly established:

1. The plasma cell is a cytomorphic variant of a number of cell types of the reticulo-endothelial system. Its life history involves alteration of the cytoplasm and of the nucleus of the parent cell type, usually in the direction of decreased size and more basophilic constitution.

2. There is an invariable relation between plasmacytosis and hyperglobulinemia in serum, in the tissues, and in tissue culture.

3. Hypersensitivity, both experimental and clinical, is associated with the development of plasma cells.

4. A cycle of maturation of the plasma cell population is initiated by anaphylactic shock.

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Chemical studies on the plasma cell have been carried out by Bing, Fagraeus, and Thorell,[1] who, applying the ultraviolet absorption spectrum technique of Casparrson, have shown the amazing activity of the nucleoprotein mechanisms in this cell. These data have been interpreted by them to indicate an endocellular secretion of antibodies by this cell type.

Our own work has shed some light on the origin of these antibody-secreting cells. In the bone marrow, in response to sensitization to bacterial or simple antigens, plasmacytosis stems mainly from the primitive reticulum.[21] We have substantiated the observations of Rohr,[26] who reported a distinguishable plasmacytic reticulum. In herpetic virus encephalitis in rabbits,[1] we have reported the formation of plasma cells from invasive lymphocytes, from microglia, from oligodendroglia, and from reticulum cells of the pia-arachnoid. Good[14] has shown the origin of the splenic plasma cell from the macrophages or reticulum cells and also from the lymphocyte. In the liver, both the von Kupfer cells and the infiltrating lymphocytes form plasma cells. The conclusion is easily drawn that all multipotent cells of the connective tissues are capable of entering, upon appropriate stimulation, the cytomorphic sequence terminating in the Marshalkó, or the mature, plasma cell. Our observations lead us to believe that once this stage is reached, pyknotic degeneration ensues and the cells disappear.

Morphologically the plasma cell is characterized by four simultaneous structural features: (1) Heavy, plaque-like chromatin aggregations in the nucleus, always with sharp boundaries (in contradistinction to the chromatin clumps seen in lymphocytes); these account for the well-known *radkern* or cartwheel nucleus. (2) Intense basophilia of the cytoplasm. (3) The presence of a clear space in the nucleus, usually in the widest part of the cytoplasm, the *hof*. (4) Marked eccentricity of the nucleus. These signs make for easy recognition of the mature stage of the plasma cell, the cell described by Marshalkó. The true import of this entity, however, is not to be understood without a consideration of the basic dynamics of inflammation. Because the plasma cell does not represent a species of connective tissue cell in the same sense that the terms lymphocyte or fibrocyte do, but rather a functional stage of any multipotent cell, its place in the economy of the body is to be sought through a careful unravelling of the physiologic significance of the alterations in structure seen in the developing plasma cell. Much has been written on inflammation, mostly in regard to the production of the macrophages which serve the body as scavenging cells. Figure 1 shows the development of phagocytic cells from the two commonest sources in adult subcutaneous tissue, the lymphocyte and the wandering cell. The lymphocyte represents the circulating form of the primitive reticulum cell and is able to invade any inflammatory site in enormous numbers. In spite of its compact form in the blood stream, a few hours suffice for the de-differentiation whereby it "unfolds" to form the intermediate polyblast. This last-

named cell is the most basic inflammatory cell. It is differentiated from the wandering cells of the subcutaneous tissues more by origin than appearance, for between this cell and the ameboid wandering cell, no significant morphological distinction exist. Ordinary inflammatory stimuli

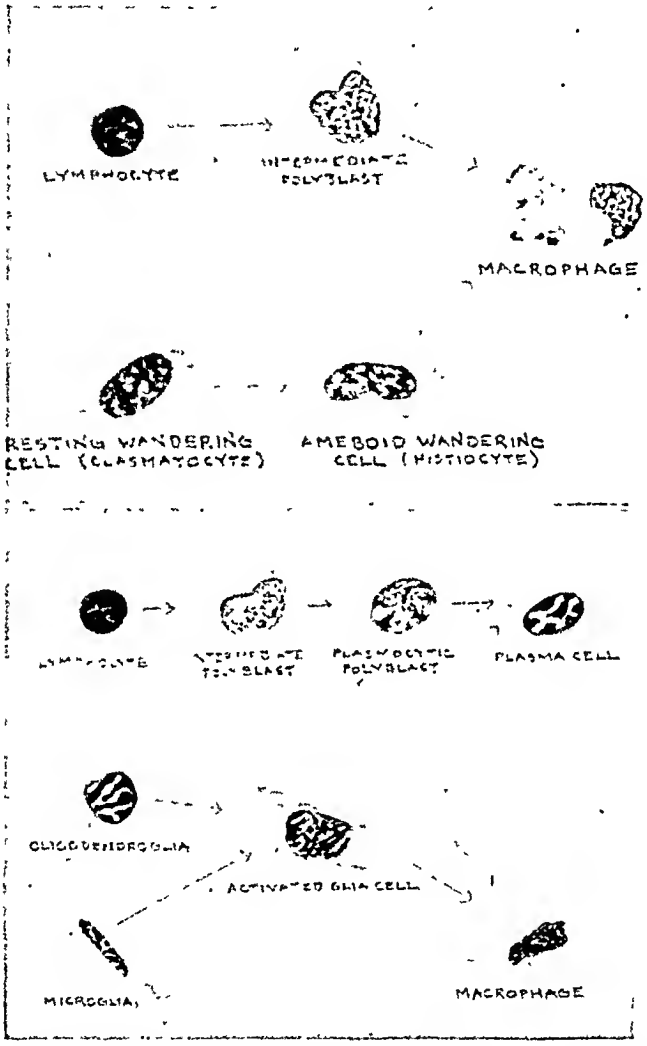


Fig. 1. *(above)* The evolution of macrophages in simple inflammation of the subcutaneous tissue. Cells are drawn from tissue spreads stained with Wright-Giemsa. For careful delineation of this and the succeeding three figures, the authors are greatly indebted to Mr. John B. Hyde.

Fig. 2. *(below)* The evolution of inflammatory cells in the brain as seen in allergic and simple inflammation. Microglia processes are from sectioned material; all other structures are shown as they appear on the brain imprint stained with Wright-Giemsa.

lead to the evolution of macrophages from these two cells, and the intense phagocytic activity of these cells apparently serves an important role in the body's reaction to an inflammatory agent.

Inspection of cytodynamics of the brain inflammatory response in herpetic brain disease leads to the discovery of a conspicuous second line of development, from the intermediate polyblast to the plasma cell (Fig. 2). The finding that this constant brain plasmacytosis was paralleled by a similar plasmacytic alteration in the bone marrow and spleen in these encephalitic rabbits showed us the importance of considering allergic mechanisms in the etiology of this disease. This led to an investigation of the effects of micro-injection of inflammatory agents into the cerebral cortex of rabbits. Minute amounts (ca. 0.01 c.c.) of egg white were injected, and observations were made on the earliest stages of inflammation. In each of the series, the first responses consisted of the formation of perivascular cuffing around the nearby blood vessels and of the activation of the glia surrounding the tiny lesion. This activation consists first of an alteration of the protein components of the cell to produce more basophilic staining of both the cytoplasm and nucleus. The microglia, whose elaboratory branched processes are ordinarily invisible in sections stained with cresyl-violet, show outlines, in some cases, similar to those revealed by the silver impregnation stains. Similar changes in the cytoplasm of the oligodendroglia are to be observed. The nuclei of the latter cell type show condensation of the chromatin and marked thickening of the nuclear membrane. As hematogenous lymphocytes invade the region from the perivascular cuffs, they undergo a transformation, the nature of which has been described by Kolouch. The cells grow in size and come to resemble more and more the intermediate polyblast described by Townsend and Campbell[28] in the connective tissue inflammation. In the inflammatory sites which were uncomplicated by the previous sensitization of the animal to the foreign material, these intermediate polyblasts mature into the active macrophages which are variously named by previous authors—compound granular corpuscles, gitter cells, et cetera. This inflammatory picture has been carefully studied and described by Dougherty.[10]

In those animals where the injected material is not simply a foreign substance but, by reason of previous sensitivity, a powerful antigen, quite a different line of maturation of these cells occurs. The intermediate polyblasts give rise to a new species of cell, a non-phagocytic polyblast which shows unmistakable plasmacytic features in nuclear structure and cytoplasmic basophily. These we have termed the plasmacytic polyblast. A noteworthy feature of this cell type is its non-phagocytic nature. These cells may then be followed for several days in the inflammatory lesion, and their progression to the Marshalkó type of plasma cell is clear. Thus the evidence is unmistakable that experimental inflammation of the brain that is complicated by antigenicity of the foreign substance is distinguished by the formation of plasma cells. In the lesions described, maturation of some macrophages from the invasive lymphocytes via the intermediate polyblast line was observed, but a definite impression was gained that there

existed an environment which, on the whole, was inhibitory to phagocyte production.

The importance of making comparable studies on the other organs was immediately apparent, and in a series of experiments on rabbits, exactly comparable pictures distinguishing allergic from nonallergic inflammation were observed following similar injections into the spleen and lymph node.

It should be remarked here that an invaluable adjunct to these studies of experimental inflammation and to the inflammatory pathology of virus encephalitis and of the Rivers-Schwentker or allergic encephalomyelitis was the use of air-dried Romanowsky-stained imprints. This technique, which was borrowed directly from hematological procedures because of the greatly superior cytological detail revealed, was a *sine qua non* to the exact tracing of cell lineage in these studies. The application of a generalized histological procedure to the study of the inflammatory cells of the brain not only rectifies the grievous damage done neurohistologically by those who would consider the brain an organ apart, whose cellular constituents could be studied only by silver impregnation and esoteric procedures, but adds an adjunct to the stained section which fulfills the need of the most exacting type of cytology. Use of such criterion as the external shape of cells and of affinity for metallic ions in complex solutions cannot lead to an understanding of the connective tissues of the brain which will be comparable to, or even commensurate with, our detailed understanding of the comparable supporting tissues of other organs.

The neurotropic viruses diseases have been studied in a thorough manner by Goodpasture and Teague,[16] Howe and Bodian,[18] Olitsky[25] and others. We know that the general pattern of this group is that of poliomyelitis in which the infectious virus serves as the causative agent and shows a proclivity to the neuron itself. Invading the nervous tissue, usually via axonic channels, the virus lives as a parasite in the nerve cell itself. Some question has been raised as to the part played in the disease by the "primary damage" done the nerve cell population by the parasitic virus. This question will not be taken up here except to note that while there is certainly strong evidence of damage and even destruction to the neurons by the primary action of the resident virus, the acute disease which is known to result from these infections is marked both clinically and histologically by inflammation of the central nervous system and is similar to the inflammatory encephalitides in which no virus is involved. In other words, we must look beyond the parasitism of the nerve cell by the virus for the essential nature of encephalitis. The problem of the origin of the inflammatory changes is the problem to which we set ourselves at the inception of this work and the one whose solution we wish to discuss.

As an experimental virus disease, we have used principally the severe encephalitis known in rabbits to follow infection with Herpes simplex

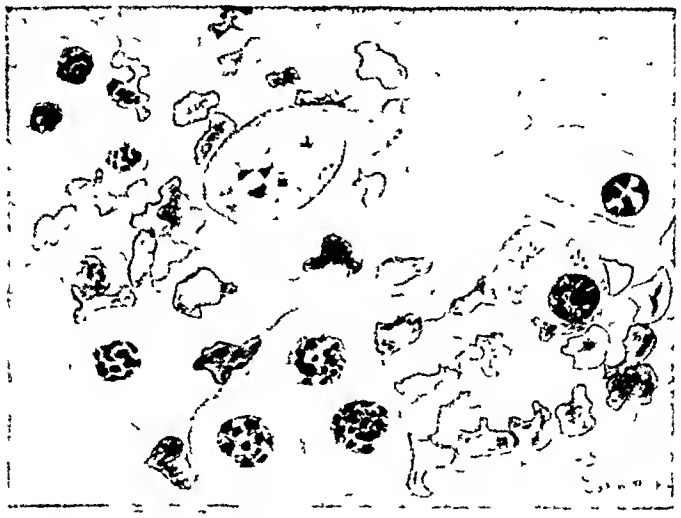
virus. Recourse to poliomyelitis in monkeys was made, and considerable information was derived from a study of brain imprints and sections of humans autopsied following death during acute poliomyelitis.

In herpetic encephalitis in rabbits the pathology of the full-blown disease presents a picture of massive perivascular cuffing throughout the brain and spinal cord, glial activation, and a large and complex population of inflammatory cells. This latter feature lends itself especially to study by means of the imprint method. All stages of lymphocytic transformation are seen. Intermediate polyblasts cloud the field and show both lines of development, to the macrophage and to the plasmacytic polyblast. The latter cell is found in great profusion and so are all the maturation stages extending to the Marshalkó plasma cell and beyond to pyknotic dwarf remains. The preparation is not, of course, suitable for a study of glial activation for these resident cells are so overshadowed by invasive cells that a clear idea of their development is impossible. A noteworthy point is the wide involvement of the reticulo-endothelial system at this stage of the disease. Stimulation of the reticulum in the spleen and bone marrow is striking, and a profound plasmacytosis of both organs is seen. This resembles the condition which we previously described as the result of bacterial and egg white sensitization.[21] At this stage, the animal has a high fever, is widely paralyzed, and subject to wild fits which alternate with profound depression.

Additional meaning is given this picture by inclusion of the earliest stages. The first symptom of disease following innoculation on the scarified cornea is an abrupt rise in temperature. At this stage, usually about three days after introduction of the virus, the changes mentioned above as characteristic of the severe disease are seen in the brain but with the mature stages of the cell lines absent. Plasma cells are scattered and immature. The intermediate polyblast is the most common cell, but the whole population of inflammatory cells is low compared with the final stages. Most interesting is the parallelism existing between the brain pathology at this stage and the alterations of the spleen and bone marrow. Here, clearly, may be seen the earliest stage of plasmacytic activation. Large reticular plasma cells are present in significant numbers, but the mature forms are scarce. Comparable examination of rabbits in somewhat later stages (by two-day intervals) shows that the changes described for the earliest disease stage progress in time so that, in both brain and in the reticulo-endothelial organs, more and more mature forms are to be found. The disease process, once started, continues also to produce new inflammatory cells, characteristic of the earlier lesions, and gradually the spectrum of the cells present is extended to include all stages.

If this pathological sequence may be interpreted as dependent upon some allergic mechanism of virus disease, it is obvious that encephalitis which is purely allergic in nature must exhibit the same. In a forthcoming paper,[5] we are describing the cytodynamics of the brain inflammation in

the diffuse allergic encephalomyelitis in guinea pigs induced by sensitization to homologous brain, utilizing bacterial adjuvants after the method of



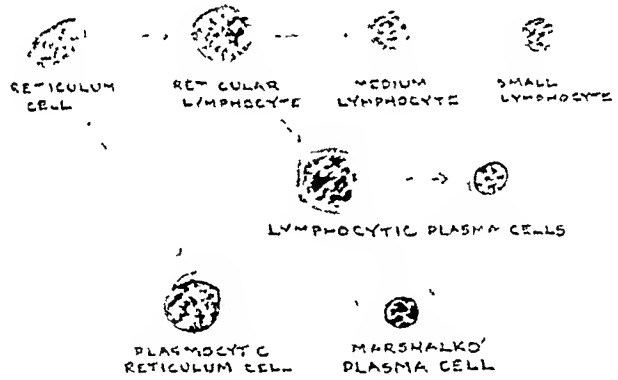


Fig 3 *(above)* Composite high powered field from imprint of brain in allergic acute encephalitis in guinea pig At top center of field is the imprint of a large neuron, showing the chromatin detail of the nucleus as well as the blue stain of the ribose nucleotides of the nucleolus and of the cytoplasm Commencing at the upper left hand corner and extending downward, across, and upward to the right are progressive stages in the evolution of the plasma cell from the invasive lymphocyte

Fig 4 *(below)* The formation of the plasma cell in the spleen as seen in allergic acute encephalitis in guinea pigs The uppermost line represents the normal lymphocytic derivation from the primitive reticulum. The lowermost line shows the origin of the Marshalkó cell from the plasmacytic reticulum of Rohr, itself a derivative of the primitive reticulum cell The middle line of development, the lymphocytic plasma cell phylum, is shown as offshoots from the reticular lymphocyte Between the latter cell and the large lymphocytic plasma cell lies (not illustrated) the plasma-blast of Moeschlin All cells are drawn from splenic imprint, stained with Wright Giemsa

Kabat, Wolf, and Bezer[19] and of Morgan.[21] In animals injected with 3.0 c c. of brain adjuvant mixture subcutaneously, a severe and usually

fatal encephalitis develops in from thirteen to twenty-four days. Weakness of the hind legs was often the initial symptom, followed in the next several days by spastic or flaccid paralysis, tremors, ataxia, nystagmus, ptosis, lethargy, and death. Cultures of the central nervous tissue removed with aseptic precautions from moribund, paralyzed, encephalitic animals showed no growth on blood agar plates, nor was success obtained in attempts to demonstrate a virus agent in the involved nervous tissue by intracranial and intraperitoneal passage in mice or guinea pigs or by intracorneal inoculation in rabbits.

The identity of the disease process is at once apparent upon examination of the imprints and sections. The enormous inflammatory cell population of the diseased brains of these guinea pigs is dominated by members of the plasmacytic line (Fig. 3). The spleen and bone marrow also reveal a magnitude of plasmacytosis which we had not previously seen. What differences strike the eye is that the alterations seem more profound in the encephalitis due to iso-sensitization. There is more involvement, in the brain, of the glia than in many herpetic rabbits, though some animals with the latter disease approach the same extent of glial activation. In the spleen, a tumorous plasmacytosis increases the size of the organ to twice its normal volume. Not only the large reticular cells of the spleen take part in the plasmacytic development. The smaller splenic lymphocytes are involved to a great extent, and the population of developing plasma cells contains many of the type of cells which Moeschlin[23] has described. These are cells intermediate between splenic lymphocytes and mature plasma cells. A similar development is to be seen in the bone marrow. One may properly deduce that the antigenic stimulation was so strong in this type of experimental disease that a wider variety of cells was induced into what one might call plasmacytic degeneration. Thus the lymphocytic plasma cell is a variant of the more ordinary reticulum plasma cell and is correlated with overwhelming antigenic stimulation. Its somewhat altered morphology is a result of its origin from a more mature type of cell than those affected by less violent antigenic stimulation. The work of Rohr and of Moeschlin, through this unifying view, appears to have no contradictory implications.

The criteria by which one operates with this type of material are those which have been built up by students of morphological hematology in their study of the cell lineage of the components of the hematopoietic organs. Rapid strides in our knowledge of the basic chemistry of cellular processes is transforming this type of study into a less empiric and more analytic interpretation. Of interest to us in this regard, in our study of the activation of reticulo-endothelial cells to form plasma cells, is the recent success of the school of Casparsson in Sweden, which has succeeded in working out, in a preliminary way at least, the importance of the nucleic acid cycle in cell metabolism. The analysis by this investigator and his

associates of the varying nucleic acid content of cell organelles in their ontogenetic development has made possible the finer interpretation of the Romanowsky stains which we have used in our imprint preparations and the cresylviolet and erythrosin staining of the sectioned material. In the study of inflammation and other tissue activation, and, in particular, of allergic inflammation, we find that the great increase in the ribosenucleic acid in the cytoplasm is a concomitant of protein synthesis at the time of antibody secretion by these cells. The copious basophilic cytoplasm which characterizes the plasma cell is a reflection of the hypertrophy of the mechanism of protein synthesis. The matter is not, however, a simple one, and the desoxyribose nucleic acid component of the nucleus and particularly the nuclear membrane undergoes concomitant changes which must have far-reaching significance in the economy of the cell, for this portion of the cell contains the genetic material. As we know, much of the predictable antigen-antibody phenomena are genetically controlled (cf., for instance, Chase[5]). The factors which cause a substance to be antigenic for one species and not for another, or (in the case of viruses) pathogenic for one species and not for another, are in all likelihood to be understood by unravelling this relationship. Certainly, there are few problems of such outstanding biological importance as that presented here by the changes in nuclear pattern of body cells induced by protein components of the environment.

At this point we must make what deductions we can with the fairly considerable body of knowledge which we now possess. The neurotropic viruses are antigenic in themselves. This we know by the specific antibody production induced by infection. It is also demonstrated that brain tissue or some fraction thereof is, under certain circumstances, a strong antigen, for allergic encephalomyelitis is a manifestation of this fact. The stimulus to plasmacytosis in the brain may be judged to be antigen exposure from the micro-injection experiments described above. Thus we may consider the pathogenic sequence of events in the case of infection with neurotropic virus as follows: The virus enters the nervous system by an axonic portal, migrates to the cell body and multiplies. Migration from one cell body to another, by a means as yet unknown, is clearly shown by many experimenters. That damage is done to the nerve cells by the resident virus is probable, but its nature is not known. At an early stage in the infection, however, the cell parasitism causes a release of an antigen into the surrounding tissue. This may be the virus itself, as seems more likely, or may be a degradation product of the damaged nerve cells; our knowledge at this point is insufficient. The effect of this antigen, whatever it is, on the surrounding tissue is clear. An inflammatory focus is set up, the resident glial cells are activated, lymphocytes migrate through the nearby blood vessels, and differentiation of inflammatory cells (intermediate polyblasts) from these two sources[10] begins. The presence of an

antigen tips the balance of the cell differentiation toward the plasma cell line. The carrying of the antigenic material from the focus of its release by the blood stream similarly activates the reticulo-endothelial cells of the bone marrow and spleen to plasmacytosis, and the changes which we have reported in early herpetic encephalitis are thus produced.

One may well question whether the time intervals which we have established for these changes are sufficient for the antigen-antibody reactions presupposed. Direct evidence on this is not sufficient to answer the question, but considerable credence is derived from the experiments of Gittner, Coolidge, and Huddleson,[12] who in 1916 showed that antibody return may be detected in the cow's udder in twenty-four hours. These findings, together with the presence of the presumed antibody-secreting cell which we report on the third day in the brain of the corneally inoculated rabbit, make one feel that such a period is indeed adequate for allergic type of pathology to develop. It is our feeling that the ideas which are widely expressed as to the slow nature of the development of allergic inflammation and antibody return are in need of drastic revision.

The problems considered here are practical as well as theoretical, and our attention must turn also to consideration of curative procedures in relation to allergic pathology. Only the matter of therapy with the use of the anti-anaphylactic drugs will be considered here. It is an obvious line of reasoning that supposes that any sequence of pathogenesis involving antigen-antibody reactions might prove vulnerable to treatment with anti-anaphylactic drugs if such drugs exist. Thus we have concerned ourselves with the drugs which are thought to have this property. Of the antihistaminics, we have only negative results to report. That they do not operate as truly antianaphylactis, in the sense demanded by this problem, we reported several years ago.[6] Our interpretation is one derived from Hochwald,[17] that the histamine release in anaphylaxis is a terminal link in a long chain of events involving antigen-antibody reactions, and its abortion with the use of these highly potent drugs like Benadryl does not get at the mechanism with which we are here dealing. All of our experiments on the use of antihistaminic drugs in encephalitis terminated in failure. The salicylates, however, have convinced us of their great promise. The work of Swift[27] and later papers of Coburn and his associates[9] led us to test the effect of acetylsalicylic acid on anaphylactic shock, and we have reported[7] our success in its prevention. In a forthcoming paper[15] we are reporting the prevention of allergic disseminated encephalomyelitis in guinea pigs with sodium salicylate and particularly with that drug used in conjunction with para-aminobenzoic acid. We have as yet no reports to make on virus encephalitis, but the striking effect which these drugs show on its pure allergic counterpart give reason to hope.

REFERENCES

1. Bing, J.; Fagraeus, A., and Thorell, B.: Studies on nucleic acid metabolism of plasma cells. Acta physiol. Scandinav., 70:282-294, 1945.
2. Bjorneboe, M., and Gormsen, H.: Experimental studies on the role of plasma cells as antibody producers. Acta path. and microbiol. Scandinav., 20:649-692, 1943.
3. Cajal, S. F.: Manual de Anatomia Patologica General. Ed. 1. Barcelona, 1890.
4. Campbell, Berry: The cell lineage of the inflammatory cells of acute encephalitis with a discussion of the significance of the plasma cell. Anat. Rec., 97:7-8, 1947.
5. Campbell, B., and Good, R. A.: Cytopathology of diffuse allergic encephalomyelitis in guinca pigs. (Unpublished manuscript.)
6. Campbell, Berry; Baronofsky, Ivan D., and Good, Robert A.: Effects of Benadryl on anaphylactic and histamine shock in rabbits and guinea pigs. Proc. Soc. Exper. Biol. & Med., 64:281-283, 1947.
7. Campbell, Berry: Inhibition of anaphylactic shock by acetylsalicylic acid. Science, 108:478-479, 1948.
8. Chase, M. W.: Cellular transfer of cutaneous hypersensitivity to tuberculin. Proc. Soc. Exper. Biol. & Med., 59:134-135, 1945.
9. Coburn, Alvin F., and Kapp, Eleanor M.: The effect of salicylates on the precipitation of antigen with antibody. J. Exper. Med., 77:173-183, 1943.
10. Dougherty, T. F.: Studies on the cytogenesis of microglia and their relation to cells of the reticulo-endothelial system. Am. J. Anat., 74:61-95, 1944.
11. Fagraeus, Astrid: Antibody production in relation to the development of plasma cells. Acta med. Scandinav., suppl. 9:1-122, 1948.
12. Gittner, W.; Coolidge, L. H., and Huddleson, I. F.: Study of the milk in bovine infectious abortion. J. Am. Vet. M. A., 50:157-167, 1916.
13. Good, R. A.: Allergic brain inflammation. A morphological study. J. Neuropath. & Exper. Neurol., (in press).
14. Good, R. A., and Good, T. A.: Early plasmacytosis of the spleen, liver, lymph node and connective tissue. Anat. Rec., 103:123, 1949.
15. Good, R. A.; Campbell, B., and Good, T. A.: Prophylaxis of allergic acute disseminated encephalomyelitis in guinea pigs with salicylate and para-aminobenzoic acid. Fed. Proc., 8:356-349, 1949.
16. Goodpasture, E. W., and Teague, O.: Transmission of the virus of herpes febrilis along nerves in experimentally infected rabbits. J. Med. Research, 44:139-184, 1923.
17. Hochwald, Adolph: Personal communication.
18. Howe, H. A., and Bodian, D.: Neural mechanisms in poliomyelitis. Pp. 1-234. New York: The Commonwealth Fund, 1942.
19. Kabat, E. A.; Wolf, A., and Bezer, A. E.: Studies on acute disseminated encephalomyelitis produced experimentally in rhesus monkeys. III. J. Exper. Med., 88:415-426, 1948.
20. Kolouch, F.: Origin of bone marrow plasma cell associated with allergic and immune states in rabbits. Proc. Soc. Exp. Biol. & Med., 39:147-148, 1938.
21. Kolouch, F.; Good, R. A., and Campbell, B.: The reticulo-endothelial origin of the bone marrow plasma cells in hypersensitive states. J. Lab. & Clin. Med., 32:749-755, 1947.
22. Michels, N. A.: The plasma cell. A critical review of its morphogenesis, function and developmental capacity under normal and under abnormal conditions. Arch. Path., 11:775-793, 1931.
23. Moeschlin, S.: Die Herkunft der Blutplasma-Zellen der Hepatitis epidemica anhand von Milzpunktaten. Gasteroenterol., 71:97, 1946.
24. Morgan, I. M.: Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue. J. Exper. Med., 85:131-140, 1947.
25. Olitsky, Peter K.: Experimental studies on the virus of infectious avian encephalomyelitis. J. Exper. Med., 70:565-582, 1939.
26. Rohr, K.: Blut-und Knochenmarksmorphologie der Agranulocytosen. Folia Haemat., 55:305-367, 1936.
27. Swift, H. F.: The action of sodium salicylate upon the formation of immune bodies. J. Exper. Med., 36:735-760, 1922.
28. Townsend, W. A., and Campbell, Berry: The effects of roentgen rays on the inflammatory cells of the mouse and rabbit. Blood, (in press).

PROTEIN AND VITAMIN METABOLISM IN THE ALLERGIC STATE

A Preliminary Study

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FOOD sensitivity is one of the most common observations of the patient in the generally allergic state. Almost any type of food is capable of producing allergic symptoms in the vulnerable individual. Among very common foods with pronounced allergenic properties are egg, milk, cheese, wheat and nuts. Familiar symptoms associated with food sensitiveness are dermal conditions such as urticaria, eczema and bronchial asthma.

Rowe,[15] in a study of 270 cases of food allergy, reported an incidence in allergic patients of 34 per cent with eczematous and/or urticarial involvement and 18 per cent with bronchial difficulties. In a screening over a period of years, of a total of 1,418 patients with bronchial asthma, this investigator found that in 57 per cent food allergy was a prominently predisposing cause.

An absolute agreement on the precise biological mechanism involved in the development of these various manfestations of food and other allergies has not yet been reached. Unquestionably, hereditary factors must be considered. Ratner[13] is of the opinion that an important means of acquiring food sensitivity is through the transmission of the allergen in utero. He has demonstrated that under certain conditions, an infant having an allergic predisposition, may be actively sensitized through the mother's overindulgence in certain protein foods during the antepartum period. This may account for the frequently observed reactions to egg white and other foods in infants upon ingesting these substances for the first time.

The theory has been presented[11] that allergy to foods is brought about by an excess of incompletely digested protein into the blood serum. According to this school of thought, this condition is due to a low concentration of pancreatic enzymes in the serum, which in turn reflects pancreatic deficiency in the intestinal tract.

Ratner,[14] in elaborating on this hypothesis, writes of the biologic specificity of proteins. Sensitization is frequently brought about by the direct introduction of proteins into the blood stream; subsequent exposures or injections produce violent reactions (anaphylaxis). Because all proteins, regardless of their type, are constructed from essentially the identical building stones (amino acids), the inference is that specie differences exist among proteins only because of variations in the organizational and quantitative amino acid make-up of the mother substances. However, the normal process of digestion autolizes all proteins, regardless of species, to a point where individual specificity of structure is no longer a factor to be considered.

Consequently, the completely nonallergic patient, if there is such an individual, is able to ingest any protein orally, without reaction, because normal digestive processes function to hydrolyze the complex structural entity into its individual amino acid and, to a certain degree, polypeptide building blocks. In the sensitized individual, it is agreed, that defective pancreatic mechanism, coupled with increased permeability of the intestinal lumen, allows the absorption of sufficient unhydrolyzed protein to produce allergic symptoms.

Directly related to the foregoing, it is known that various foods to which the patient has been sensitized, can be rendered hypo-allergenic by heat and pressure applied in preparation. It is a known clinical fact that allergenic foods, not tolerated when raw, may be eaten with impunity when cooked. Ratner and Gruehl[11] showed that in guinea pigs, evaporated or boiled milk was considerably less antigenic than fresh milk. In infant feedings, we observe often that the lesions of eczematous babies are cleared up, at least partially, when the formula is changed from fresh to evaporated milk. It has been theorized that the heating and pressure used in the preparation of these foods succeeds in virtually starting the protein digestion process in the cooking pot or vat, i.e., from primary proteins to secondary, or possibly to proteoses or even peptones. Thus the burden thrown upon the deficient digestive mechanism of the allergic child or even adult may be eased in some cases, with toleration and cessation of symptoms brought about. Other prepared foods found to be allergenically altered are cooked cereals, melba toast, popcorn, dextromaltose, noodles and spaghetti.

Unfortunately, relief of symptoms in these patients by precooking or special preparation of allergenic foods is the exception rather than the rule. In a great majority of instances during the diagnostic period, drastic elimination from the diet of all offending foods, both known and suspected, is the indicated procedure. After complete diagnosis has been effected, a modified elimination diet is instituted for an indefinite period or permanently. In formulating such diets, it is of extreme importance to consider the dietary nitrogen allowance of the patient because typical elimination schedules, especially for the severe allergic individuals, are often notoriously deficient in proteins[16] and vitamins.

The use of protein hydrolysates during these distressing periods has been employed with promising results by several investigators. Shohl et al.,[18] in treating infants with severe milk allergies, were able to provide positive nitrogen balance in these cases by the use of oral hydrolysates. Hill[3] reported on thirty-six milk-sensitive, eczematous infants who were given protein hydrolysate for prolonged periods (up to three months) to satisfy protein requirements. In many of these cases, the hydrolysate feedings were well tolerated, the eczema subsided and good weight gains were recorded. From these results, this clinician concluded that the protein hydrolysate mixture was the preferred milk-free food for sensi-

tized patients. Olmsted[12] has employed amino acids during the prolonged diagnostic period in severe food allergy; he found that the usual starvation, with its depleting effects, could be largely averted by these means.

Other nutritional studies, including the use of vitamins, especially the entire B complex in the treatment of atopic eczema, have been reported. For example, Kristensen and Vendel,[7] in intensive studies of chronic and acute eczema in twenty patients, found that the vitamin B complex found in yeast was quite effective in treatment. Harris and Gay[2] have checked these results with the employment of extracts of large amounts of both liver and yeast in treatment.

As reported in the foregoing, the nutritional attack in allergic states represents a provocative but logical therapy and is worthy of further and more intensive investigation. Nutritional factors, administered in easily assimilable forms and in amounts appreciably in excess of minimum daily requirements, will provide raw materials for quick tissue building and repair and also may conceivably furnish potentiating influences tending toward increased magnitudes of detoxication and immunologic mechanisms, so important to consider in the study of degenerative processes taking place in the allergic patient. Thompson's work,[19,20,21] demonstrating the effective detoxication properties of nutritional elements, substantiates this concept. This worker, through exhaustive animal studies, has found that subjects placed on high nutritional levels produced by large quantities of vitamins and amino acids, and subsequently given several times the minimum lethal dose of agents such as gold, mercury, sulfa compounds, guanidine and histamine, were much better equipped to tolerate these toxic substances than control animals without nutritional fortification.

Vermilye, in a paper to be published, notes that in a group of animals sensitized to horse serum, the subjects fortified with enzymatic protein digests and vitamins survive the shock dose of the antigen with no evidence of tissue necrosis, while the unprotected subjects die with typical Rich lesions, hemorrhage, edema, thrombosis or fibrinoid collagen degeneration. It has been theorized by Miller et al[9] and Neale et al[10] that a detoxication agent, by oxidation, reduction and subsequent conjugation with an antigenic substance, causes it to be excreted as a harmless nontoxic by-product. It may be hypothesized that in allergy this mechanism functions conspicuously in providing protection against an antigenic process with its typical allergic manifestations.

THERAPY

The attempts at the successful management of allergic patients using conventional symptomatic treatment, elimination diets and/or topical medication have been generally disappointing. The nutritional and detoxication approach, because of encouraging preliminary studies described in the foregoing, has stimulated the writer to attempt the general management and control of patients with allergic eczema and bronchial asthma

by intensive nutritional therapy. In the review of previous work it has seemed evident that while reports of success in treatment in some instances were spectacular, much was to be desired in terms of requirements in a complete nutritional schedule. It seemed illogical to employ protein hydrolysates without concomitant vitamin therapy and vice versa. Jacobson[4] and Ruskin[17] have pointed out a distinct nutritional interrelationship between amino acids and vitamins, and have stated that the complicated coenzyme systems built up from their co-ordination are necessary for the formation of the respiratory enzymes, from which good growth and energy are provided and maintained. These workers state that either amino acids or vitamins represent only one phase of the system and alone are relatively inactive biologically. They feel, consequently, that patients who require vitamins are those likely to be lacking also in amino acids. Thus, in formulating our complete nutritional regimen for therapeutic management in our cases, we have taken these advanced ideas into consideration and have included the following distinct entities into the treatment:

1. A protein hydrolysate, derived from primary nutritional Brewer's yeast.* This material contains a full and balanced complement of all the essential amino acids plus polypeptides. We believe that a partially autolyzed protein, i.e., an hydrolysate, is important because certain valuable factors, such as strepogenins, are present only before the protein finally goes to the amino acid stage—in other words, in a partially hydrolyzed form. Therefore, we believe that a protein mixture composed solely of amino acids will be deficient because of the lack of strepogenins and other possibly significant factors. This protein digest used has a very high biologic value, is virtually sodium free and shows a high potassium ion value. Furthermore, in itself, it is a fairly rich source of the whole vitamin B complex.

2. A rich natural source of the entire vitamin B complex, derived from whole liver concentrate, rice polishings, Brewer's yeast, wheat germ and unprocessed honey.** It is believed to be important that a source of B complex activity be derived from natural substances rather than from combinations of synthetics.[5,8]

3. An oil-in-water emulsion*** containing therapeutic quantities of all

*Protein Hydrolysate-MRT.

**Elixir Vitamin B Complex-MRT, containing the following assay: Each teaspoonful (5 c.c.) derived from 8.0 gm. fresh liver, 7.2 gm. rice bran, 2.5 gm. dry Brewer's yeast, 1.0 gm. defatted wheat germ and 0.5 unprocessed honey, contains a potency as stated:

Vitamin B_1 (thiamine)	2 mg.
Vitamin B_2 (riboflavin)	3 mg.
Niacin and niacinamide	20 mg.

plus pyridoxine, pantothenate, folic acid, B_{12}, thymine, choline, biotin, inositol and all other factors of the whole vitamin B complex.

***Emulsion Multivitamins-MRT, containing the following potency per teaspoonful (5 c.c.):

Vitamin A	25,000 U.S.P. units
Vitamin D	2,000 U.S.P. units
Vitamin B_1	5.0 mg.
Vitamin B_2	10.0 mg.
Vitamin C	150.0 mg.
Niacinamide	100.0 mg.

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CASE HISTORIES

Cases 1 and 2 (Severe Bronchial Asthma).—The patients were two white men, fifty and fifty-five years of age respectively, both of whom presented histories of bronchial asthma of allergic etiology over a period of more than fifteen years. These patients had been under the constant care of various physicians. During the interim period, symptomatic treatment had been instituted, including frequent injections of epinephrines. Skin tests presented contradictory results. These patients had had treatment with house dust and vaccine; neither patient was sensitive to pollen or grass.

The patients were admitted to the hospital one day apart. They were seen initially in a status asthmaticus and were epinephrine-fast. After forty-eight hours of usual treatment—intravenous glucose-saline, aminophylline, et cetera—the acute symptoms subsided but asthma persisted, responding only to frequent epinephrine and aminophylline by vein. Relief would follow for 1 to 3 hours. At no time was the chest in either patient even moderately free of asthmatic wheezing. Chest plates were negative except for the usual findings in long standing asthma.

After seven days of the foregoing procedure, protein-vitamin therapy, as described, was instituted. All medication, except rectal aminophylline, seconal and amytal at night, was discontinued. The diet consisted solely of the "basic three" mixture, taking six to eight, 2-ounce doses throughout the day. This intensive regimen was continued for fourteen days, with improvement observed almost immediately—in one patient within three days, in the other in five. Asthma subsided almost completely in the fourteen-day period; the patients were then placed on a normal diet with the number of doses of the therapeutic nutritional formula reduced proportionately. These patients were discharged soon after; they are at home now and working at their daily occupations. They take no medication except the limited number of doses of the nutritional mixture and an occasional Tedral tablet. There have been no recurrences during the past eight months, and the patients are experiencing real comfort for the first time in their lives.

Case 3 (Atopic Eczema).—E. M., a white man, aged thirty-six, with a history of atopic allergy since childhood, was first seen in 1944 because of active flare-up of eczema. The eczema was associated with severe pollen asthma. Under usual care (symptomatic and attempts at desensitization) the asthma subsided, but the eczema became progressively more severe, involving the face, ears, chest, arms, hands and legs. He was confined to bed for several weeks on three occasions. The last severe attack was one year ago, and he was ordered to bed and started on the "basic three," six 2-ounce mixtures daily. Improvement was noted in two weeks. The itching subsided, and the skin started to heal after four weeks. In eight weeks, the skin had returned to almost normal appearance. The patient was placed on a full diet, taking foods he hadn't been able to eat for twenty years.

There has been no recurrence to date. The patient is still on the "basic three," in reduced quantity: one 2-ounce mixture daily. He gained 16 pounds in the past year, and is able to do a full day's work. He can also wear wool, which had previously caused intense itching.

Case 4 (Atopic Eczema).—A. O., a white woman, aged thirty-five, weighing 80 pounds, with a history of atopic eczema since early childhood, was first seen in October, 1936, because of severe asthma, precipitated by new living-room furniture. The asthma was curtailed (symptomatically). She had three attacks of status asthmaticus in the following five years, necessitating hospitalization. Associated eczema became progressively worse. She had been to every large clinic in New York City and had every known treatment: elimination diets, vaccines, x-ray and

played repeatedly a low content of unsaturated fatty acids in their blood sera. Of most prominence in this study were linoleic and arachidonic acids. Treatment with cod liver oil, linseed oil, corn oil and lard produced remissions in these cases.

In future studies we are considering the inclusion of therapeutic lipids, such as lecithin, along with antioxidant substances, including the tocopherols.

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REFERENCES

1. Hansen, A. E.: Proc. Soc. Exper. Biol. & Med., 41:205, 1939.
2. Harris, A., and Gay, L. M.: J. Allergy, 14:182, 1943.
3. Hill, L. W.: J.A.M.A., 116:2135, 1941.
4. Jacobson, M.: New York State J. Med., 45:2079, 1945.
5. Jolliffe, N.: J.A.M.A., 129:613, 1945.
6. Kramer, B.: Am. J. Dis. Child., 77:543, 1947.
7. Kristensen, K. P., and Vendel, S. N.: Lancet, 1:170, 1940.
8. Lewey, F. H., and Shay: Dietotherapy. P. 850. Philadelphia: W. B. Saunders and Co., 1945.
9. Miller, et al: Am. J. M. Sc., 1:300, 1940.
10. Neale, et al: J. Pharm. & Exper. Therap., 62:127, 1938.
11. Oelgoetz, A. W., et al: Am. J. Digest. Dis., 1:730, 1934.
12. Olmsted, W. H.: Arch. Int. Med., 73:341, 1944.
13. Ratner, B.: Am. J. Dis. Child., 36:277, 1928.
14. Ratner, B., and Gruehl., H. L.: Proc. Soc. Exper. Biol. & Med., 31:559, 1934.
15. Rowe, A. H.: South M. J., 28:261, 1935.
16. Rowe, A. H.: Elimination Diets and the Patient's Allergies, p. 141. Philadelphia: Lea and Febiger, 1941.
17. Ruskin, S. L.: Am. J. Digest. Dis., 13:110, 1946.
18. Shohl, A. T., et al: J. Pediat., 15:469, 1939.
19. Thompson, M. R., et al: Exper. Med. & Surg., 1:1, (Feb.) 1943.
20. Thompson, M. R.: Arch. Int. Med., 69:662, 1940.
21. Thompson, M. R.: Ann. Int. Med., 1:18, (Jan.) 1943.

THE CLINICAL APPLICATION OF A NEW PIPERAZINE COMPOUND

(Continued from Page 465)

10. Castillo, J. C.; Jaros, S. H., and de Beer, E. J.: A pharmacological study of N-methyl-N'-(4-Chlorobenzhydryl) piperazine dihydrochloride. A new antihistaminic. (In press.)
11. Dale, H.: Antihistamine substances. Brit. M. J., p. 281, (Aug. 7) 1948.
12. Editorial: Too many drugs? J.A.M.A., 139:378, 1949.
13. Farmer, L.: Evaluation of the histamine intradermal test as a general indicator of allergy. J. Allergy, 16:44, 1945.
14. Feinberg, S. M.: Conference on antihistaminic agents in allergy. New York Acad. Sci., (Oct.) 1947.
15. Friedlaender, S., and Feinberg, S. M.: Histamine antagonists. III. The effect of oral and local use of B-dimethylaminoethyl benzhydryl ether hydrochloride on the whealing due to histamine, antigen-antibody reactions, and other whealing mechanisms. J. Allergy, 17:129, 1946.
16. Friedlaender, A. S., and Friedlaender, S.: Correlation of experimental data with clinical behavior of synthetic antihistamine drugs. Ann. Allergy, 7:83, 1949.
17. Lewis, T.: Blood vessels of the human skin and their responses. London: Shaw & Sons, Ltd., 1927.
18. Perry, D. J.; Falk, M. S., and Pillsbury, D. M.: A comparison of the effect of antihistaminic drugs in human subjects by means of histamine iontophoresis. J. Invest. Dermat., 11:461, 1948.

elevations of temperature, up to 102° F. There was recurrence of the eruption in the intertriginous areas, which necessitated another week of hospitalization. She was readmitted several months later, in February, 1948, because of a dermatitis of the scalp and severe cervical lymphadenitis. At this time she exhibited oozing, crusting of the face and scalp. She was given sulfadiazine by mouth, and developed a typical drug fever, which promptly subsided, when the drug was stopped. She was discharged in fair condition after two weeks of hospitalization.

We feel that these two patients developed their cutaneous reaction on the basis of sensitivity to penicillin. In the case of the woman, the prompt flare-up on readministration of penicillin seems to be a reasonable explanation. In the case of the man, we feel that the explanation of the negative patch test is that the patient's skin was in a refractory state, a condition not uncommon following extensive and severe eruptions. The subsequent flare-up was due to absorption of penicillin from the patch test.

These two patients demonstrate the necessity of handling such generalized eczematous penicillin reactions with care. We feel that testing such individuals for cutaneous sensitivity is a procedure (whether it be patch, scratch or intradermal) that is more dangerous than useful, and it may nullify long periods of previous laborious therapy. For this reason, we did not subject the second patient to testing. Secondly, penicillin, in these cases, only initiated a cutaneous reaction, and our patients developed a broadening of their allergic base quite rapidly to a variety of topical medicaments and other drugs.

We feel that the treatment of individuals with a generalized eczematous reaction should minimize the development of multiple sensitivity. To this effect all drugs with a high index of sensitization should be avoided, unless there is a special indication. Also, we feel that our two cases demonstrated that this cutaneous reactivity and multiple sensitivity did not diminish over a period of twelve months.

REFERENCES

1. Bauer, G. H.: Allergic dermatoses complicating penicillin therapy. Arch. Dermat. & Syph., 54:292, (Sept.) 1946.
2. Epstein, S., and Pinkus, H.: Penicillin dermatitis based on tuberculin-type sensitivity. Ann. Allergy, 4:186, (May-June) 1946.
3. Farrington, J., and Tamura, J.: Cutaneous testing in a case of exfoliative dermatitis caused by penicillin. Arch. Dermat. & Syph., 56:807, (Dec.) 1947.
4. Goldman, Leon, Friend F., and Mason, L. M.: Dermatitis from penicillin. J.A.M.A., 131:884, (July 13) 1946.
5. Gottschalk, H. R., and Weiss, R. S.: Epidermal sensitivity to penicillin. Arch. Dermat. & Syph., 53:365, (April) 1946.
6. Mendell, T. H., and Prose, P. H.: Severe allergic reactions to penicillin. Am. J. M. Sc., 212:541, (Nov.) 1946.
7. Nolan, D. E., and Pedigo, Jr.: Exfoliative dermatitis following penicillin therapy. Ann. Int. Med., 25:725, (Oct.) 1946.
8. Rostenberg, A., Jr., and Welch, H.: A study of the types of hyper-sensitivity induced by penicillin. Am. J. M. Sc., 210:158, (Aug.) 1945.

BRONCHIAL ASTHMA CAUSED BY THE INHALATION OF WOOD DUST

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IT is well known that some persons on handling certain woods develop dermatitis caused by direct physico-chemical action, allergic sensitization or both. A large variety of woods have already been shown to be responsible for this condition (Senear[9]).

Respiratory allergy, however, caused by the inhalation of wood dust has been less frequently reported. It is not impossible that the etiological relationship of the condition and the wood has sometimes escaped recognition.

Rosenbloom,[7] quoting Walker,[11] described two cases of asthma in jewel polishers who respectively became sensitized to the dust from boxwood and from orangewood which they used in their work.

Bahn[1] reported allergic respiratory symptoms due to pinewood in a sawmill worker in whom positive reactions were obtained on skin testing with an extract of the wood. Desensitization was not attempted, as the procedure was considered too long and uncertain in its effects. He quoted seven other cases from the literature in sawmill workers which were diagnosed as pneumoconioses as their allergic basis had not been recognized.

In a discussion on cedar pollen hay fever, Schonwald[8] described three cases of asthma from the cedarwood itself. The patients were: a bookkeeper in a sawmill, a woodworker in another sawmill and a manufacturer of coffins. The asthma occurred when cedarwood was handled or worked. No reactions were obtained to skin tests and no beneficial results followed treatment. At least a dozen cases of this type were subsequently seen.

Stier[10] also described the treatment of a case of asthma in a man of seventy-two years, working with cedar shingles, in whom definite relief was obtained. In another patient of his, however, only partial relief followed.

Markin[5] described another case of asthma due to boxwood dust in a man of thirty-four years who had been a watchmaker for fifteen years. Although skin reactivity was not lessened after a short course of desensitization with extracts of the wood, the patient developed a gradual tolerance to boxwood and enjoyed complete freedom of symptoms.

Cobe[2] saw two patients with bronchial asthma associated with sensitivity to the dry needles of fir trees (*Picea mariana*) used as Christmas trees.

Coca, Walzer and Thommen[3] pointed out that woods were not infrequent causes of atopic symptoms in occupations involving their handling and sawing and that sawdust may be conducive to the production of asthma, not only because of the irritation to the bronchi produced by its constant

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inhalation but also because of its action as a specific atopen. They included mahogany, birch, cedar, tamarack, pine, boxwood, orangewood as etiological factors in certain cases of asthma.

Senear[9] emphasized that although the majority of woods generally produced dermatitis, reactions could also occur in parts of the body other than the skin. The mucous membranes were frequently attacked, and conjunctivitis, sneezing, increased nasal secretions, dyspnea, bronchitis, asthmatic and influenzal attacks were the commoner manifestations. He was of the opinion that the toxic agents involved were alkaloids or nonsaturated resinous acids in a free state. Davidson[1] described an irritation of skin surfaces which occurred in nearly all of more than fifty men engaged in manipulating iroko (*Chlorophora excelsa*) wood in a machine shop. The symptoms in some of the cases were more severe, and in addition to the skin condition there were manifestations of acute coryza, headache, pharyngitis, as well as chest symptoms including retrosternal oppression, a feeling of constriction and dyspnea and dry cough.

Piorkowski,[6] describing an outbreak of dermatitis in East Africa in Indian workers handling tropical woods, referred to one of five cases where catarrhal conjunctivitis and also rhinitis occurred.

DESCRIPTION OF A CASE OF BRONCHIAL ASTHMA

The following description of a case of asthma due to the inhalation of wood dust is given in detail because of numerous points of interest and because therapeutic desensitization was successfully carried out.

In September, 1946, a colored man, aged twenty-nine years, a cabinet maker by trade, living in Johannesburg, was referred to me by Dr. E. L. Fisher for investigation with regard to his asthma.

The patient's mother and maternal grandfather, both of Bantu origin, were asthma sufferers. His father, who was of Chinese stock, had never complained of any illness of an allergic nature. His two young children, one year and three years old, had not exhibited allergic symptoms.

The patient had been a cabinet maker since 1934 and was in good health until 1940, when attacks of sneezing and running of the nose began to worry him. At night his chest became constricted and he developed difficulty in breathing, with wheezing.

It is important to observe that before the outbreak of war the woods generally used in cabinet works in South Africa were imported from overseas and included walnut, Burma teak and mahogany. It was only after the war had commenced, when importation difficulties arose, that certain timbers of African origin were employed in the trade. The beginning of the patient's troubles coincided with this change in the woods used in the factory. He was compelled to leave the factory he was then working in because of persistent attacks of asthma. His attempts to work in other cabinet-making factories were equally unsuccessful.

The patient had worked for five months in the factory at the time of his visit to me. For the first three months he remained free from attacks, and then his asthma recurred. The woods used in the factory were kejaat, mvuli, partridge, Western cedar and "Congo hardwood."* The following details of these woods were

*"Congo hardwood" was the name by which a certain type of wood was known to the patient. The identity of the wood, unfortunately, could not be determined.

The patient also worked with Cape pine and embuya (*Phoebe porosa*) but, as he knew from experience that he was not clinically sensitive to these woods, extracts therefrom were not made for testing purposes.

It is of interest to note that some of the patient's fellow workers in the factory developed contact dermatitis from embuya.

An attempt was now made to desensitize the patient. For this purpose a combined extract of the woods to which he had given positive skin reactions was prepared as follows:

Kejaat	4 parts
Congo hardwood	3 parts
Western red cedar	2 parts

Before therapeutic desensitization was actually commenced, the patient's sensitivity to the combined extract was elicited by intradermal skin tests, using a series of graded dilutions. The following were the results of the tests:

Dilution	Reaction
1:10,000,000	±
1:1,000,000	++
1:100,000	+
1:10,000	+ (with some local itching)
1:1,000	+++ (typical wheal with pseudopodia)

The patient was not further tested with stronger extracts in view of the possibility of the occurrence of constitutional reactions.

Therapeutic desensitization, by the intradermal method, was commenced with the 1:1,000 dilution of the extract, and the subsequent doses administered are shown hereunder:

Date	Dose	Extract Dilution
Oct. 22, 1946	0.2 c.c.	1:1000
Oct. 26, 1946	0.2 c.c.	1:1000
Oct. 29, 1946	0.3 c.c.	1:1000
Nov. 2, 1946	0.3 c.c.	1:1000
Nov. 5, 1946	0.3 c.c.	1:1000
Nov. 12, 1946	0.3 c.c.	1:1000
Nov. 19, 1946	0.3 c.c.	1:1000
Nov. 22, 1946	0.1 c.c.	1:100
No injection during vacation period		
Jan. 27, 1947	0.1 c.c.	1:100
Jan. 30, 1947	0.1 c.c.	1:100
Feb. 3, 1947	0.2 c.c.	1:100
Feb. 12, 1947	0.2 c.c.	1:100
Feb. 19, 1947	0.2 c.c.	1:100

At this stage the patient reported that he had been free from asthmatic attacks for about two months although his working environment had remained the same, with no change in the woods handled by him in the factory. On one occasion only was there slight constriction in the chest which he described as "hardly an attack" and which soon passed off. At no time was an attack of asthma experienced during the day while at work. At most there was very occasional sneezing with slight wheezing, but even these mild manifestations disappeared within a very short time. The patient had not lost a single day's work since December. He now cycled to and from his work and no longer developed asthma even on the return ride home when he was fatigued after his day's activities. His appetite had improved, and he looked forward to his meals with relish.

It was decided to give the patient further maintaining doses of the wood extract at gradually increasing intervals, thus:

Date	Dose	Extract Dilution
Feb. 26, 1947	0.05 c.c.	1:10
Mar. 12, 1947	0.05 c.c.	1:10
April 2, 1947	0.1 c.c.	1:10

ALLERGIC ARTHRITIS

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IT is the purpose of this paper to review briefly the pertinent literature on the subject of allergic arthritis and to report three additional cases.

It was Solis-Cohen[21,22] who reported the relationship between allergy and joint manifestations. He termed it angioneural arthritis and correlated the allergic—personal and family history—food and drug hypersensitiveness with the arthropathies. Lewin and Traub[12] reported a case of delayed allergic synovitis as a result of the ingestion of English walnuts. Berger[1] described a case of intermittent hydrarthrosis in a patient having concomitant gastrointestinal allergy and urticaria. Relief of all joint symptoms was obtained by the elimination of the offending allergens from the diet. Service[20] also reported on hydrarthrosis of allergic origin. Turnbull[23] obtained positive skin reactions in patients with arthritis. Eliminating the suspected allergens from the diet improved the arthritis. He therefore regarded it as an expression of an allergic state. He refers to the variability of the skin tests and their re-evaluation during the time the patient is on an elimination diet. Kahlmeter[11] refers to a series of cases in which gastrointestinal disturbances were followed by joint symptoms. He believed it to be the result of an underlying allergy. Freund[7] noted the relationship between allergic arthritis and the ingestion of certain foods. Pottenger[19] summarized a study of his arthritic patients, and demonstrated that almost all of them had an associated allergy. Vaughn[24] was also one of the protagonists of the theory that the arthropathies might be an allergic manifestation. He reviewed arthritis in a series of 1,000 allergic patients. He came to the conclusion that food allergy played a role in allergic patients exhibiting intermittent joint symptoms, especially if there was an associated allergy in the individual or family history. Boemer[2] stated that allergy might be the etiology in his arthritic patients. Allergic arthritis was reported by Wingfield,[25] Cain,[3] Hopkins and Richmond,[10] and Paul and Logan,[15] in which the Brucella agglutination tests were negative. Palindromic arthritis with psychogenic factors related to the attacks was reported by Ferry,[6] Mazer,[13] Cain,[4] Neligan,[14] Paul and Carr,[16] and Paul and Logan.[17] Criep[5] cites a number of cases exhibiting joint disturbances and concomitant urticaria, angioneurotic edema or migraine. He notes the presence of positive skin reactions and passive transfer tests, together with a positive family and personal history of allergy. Symptomatic relief was obtained in these cases by excluding the offending allergens. Hench and Rosenberg[9] probably contributed much to the re-kindling of interest in allergic arthritis. They do admit the absence of conclusive proof that allergy may be the sole and important

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TABLE I. CLASSIFICATION OF ALLERGIC AND NONALLERGIC ARTHROPATHIES

Allergic	Nonallergic
1. Serum Allergy Due to foreign serum or drugs	1. Specific Infectious Arthritis Due to specific microorganism T.B. Syphilis G.C. Pneumococcus
2. Schonlein's purpura a. Skin eruption b. Joint symptoms	2. Atrophic arthritis
3. Intermittent hydrarthrosis Extravasation of fluid into a joint	3. Hyperthrophic arthritis
4. Palindromic arthritis (?) Intermittent inflammation of the joints, of a reversible nature.	4. Trauma
5. Bacterial arthroses Of questionable allergic etiology. Arthritis of rheumatic fever?	5. Gout

factor in allergic rheumatism. Their outstanding work points out the possibility of a definite clinical and pathological picture and mentions the etiological possibilities of allergy. Their points of discussion against the allergic hypothesis certainly do not negate its etiological significance. Additional reports and studies have been made by Grego and Harkins,[8] Perl,[18] and Wolfson and Alter.[26] The above review indicates that there is ever increasing evidence to support the hypothesis that certain arthropathies are due to an underlying allergy. In Table I a classification of the allergic and nonallergic arthropathies is suggested.

CASE REPORTS

Case 1.—Patient R. A. W., a woman aged eighteen, had been treated for arthritis of the right knee since four years of age. The tonsils and adenoids were removed at that time in an attempt to cure the arthritic condition. The patient was symptom free until eleven years of age, at which time the symptoms recurred with swelling, pain and limitation of motion. Studies by an internist, roentgenologist and orthopedist were negative. At fourteen years of age there was another remission, and x-ray studies again were negative. In April, 1946, swelling of the left knee appeared during a siege of the measles. Orthopedic shoes and treatment were prescribed without relief. The condition reappeared in December of 1946, and had a periodic recurrence since then. The attacks were characterized by slight redness and swelling, pain and stiffness of the joint, producing limitation of motion but not necessitating bed rest. The episodes occurred periodically, usually lasting three to four days, then disappearing, only to recur in an almost regular cycle every four to five days. The only joints involved were the right and left knee joints. The area around the knee was never hot.

During the acute attack there was no fever and no constitutional symptoms. It was never preceded by an upper respiratory infection. It was not affected by season, weather or salicylates. The blood studies, blood count, Wassermann reaction, and x-ray were normal. Eosinophiles were not present in the blood. A nasal smear showed occasional eosinophilia. The patient had no known food or drug allergies. Her menstrual cycle was fairly regular. During very early childhood the patient had atopic dermatitis. At present she had a mild perennial allergic rhinitis. She never had chorea or symptoms of rheumatic fever. A maternal grandfather had asthma. A maternal aunt had hay fever and asthma.

In view of the past history of atopic dermatitis and present rhinopathy, together with an allergic family history, allergic studies were suggested. Skin tests performed by the intradermal method revealed positive skin reactions to milk, potato, tomato, cantaloupe, carrots, lemon, mushroom, strawberry, and fig. Repeated

X-ray studies, orthopedic and medical consultations were negative. The patient was placed on an exclusion diet, boiled milk, and Neo-Antergan, 50 mg. four times daily. A definite improvement was noted, and the swelling, pain and limitation of motion subsided.

After two years of follow-up, the patient continues to do well. The foods which have been excluded have been reintroduced into the diet, and the patient now takes an occasional Neo-Antergan tablet.

Case 2.—W. S., a man aged forty-six, first complained of joint pains with swelling of the ankles in 1929. The attacks were intermittent in character, recurring every 3 to 7 days and accompanied by excruciating pain in the calf muscles. Removal of tonsils, adenoids, and a number of suspected teeth did not relieve the joint symptoms. In 1933, he began having intermittent massive swellings of both knees, with pain and evidence of joint effusion. The patient was hospitalized and discharged without any positive findings. In 1939, he had a recurrence of an old acne. Gold therapy was instituted, which improved the arthritis but did not aid the skin. The patient received the benefit of allergic studies on two different occasions. They were both negative except for a reaction to pork and tomato. Elimination of the pork and tomato from the diet did not improve the arthritis. Routine laboratory work including blood count, blood sugar, uric acid, blood Wassermann and Kahn tests were normal. A nephew had hay fever. In 1938, the patient noted inflammed, tender areas over various superficial parts of the arms and legs that lasted three to four days and subsided, only to recur about every two months. In 1945, another examination revealed small, very tender, poorly circumscribed, cutaneous nodules, averaging about the size of a kidney bean, on the arms and legs. A cutaneous nodule was removed for biopsy, and submitted to the pathologist.

The pathological report was as follows: "On microscopic study the specimen consisted of a large subcutaneous granulomatous nodule, in the center of which is a blood vessel. The wall of this blood vessel is infiltrated with lymphocytes and large mononuclear cells. Surrounding it there is some necrosis, and part of the vessel wall is also necrotic. Surrounding this vessel and the narrow zone of necrotic tissue there is a wide zone of infiltration, in which large mononuclear cells are arranged in palisade form, and between them are present lymphocytes and degenerated polymorphonuclear leukocytes. In the surrounding region many of the blood vessels show endarterial proliferation and are surrounded by an infiltration of lymphocytes and large mononuclear cells as well as occasional polymorphonuclear leukocytes." The absence of any eosinophiles was noted, which is rather unusual in typical periarteritis nodosa. However, the remainder of the picture is that of a diffuse vasculitis of the periarteritis nodosa type.

Case 3.—Patient A. G., a man aged thirty-two years, had arthritis for the past four years. This consisted of periodic attacks of swelling, pain, and limitation of motion of both knees. The attacks occurred regularly, usually lasting five to seven days, then disappeared completely, only to recur about every 10 to 14 days. During an acute episode the knee joint was found to transilluminate and was subsequently aspirated. Agglutination tests for Brucella and Strep. hemolytica were negative. Culture of the joint fluid proved to be sterile. X-ray of the knee suggested the presence of free fluid. Laboratory studies including sedimentation rate and uric acid were normal. Allergic studies were negative. The patient was placed on an elimination diet without relief of symptoms. The blood count on various occasions revealed an eosinophilia of 8 to 12 per cent. The personal and family history was negative for allergy. At the present writing, the joints continue to swell in a somewhat regular cycle.

DISCUSSION

Three cases of allergic arthritis have been presented. The first case had features quite similar to those described by Hench and Rosenberg as palindromic rheumatism. Case 2 was one of intermittent hydrarthrosis and panvasculitis of the periarteritis nodosa type. The third dealt with intermittent hydrarthrosis and a persistently high eosinophilia.

Palindromic arthritis is an intermittent swelling of the joint and periarticular structure. It involves both the small and the large joints, and one or more joints may be affected at the same time. The attacks occur regularly, usually lasting three to four days, then disappear completely without any sequelae, only to recur in a fairly regular cycle, about every five to ten days. During the acute episode there is slight redness, swelling, pain and stiffness of the joint with a variable amount of limitation of motion. There is no fever or constitutional symptoms. It is not affected by season, weather or salicylates. There is an absence of joint effusion or, when present, it is very slight. The fluid is sterile. Laboratory studies including blood chemistry, sedimentation rate, Wassermann test and x-ray are normal.

When the disease occurs in a patient having a concurrent allergic manifestation and a positive family history of allergy, suspicion is aroused as to its allergic possibilities. It is in these patients that an allergic investigation is of value. The etiologic specificity of the suspected allergen may be proven by skin tests and passive transfer reactions. It is further corroborated by therapeutic or clinical trial. It is rather striking to note that after innumerable attacks over a period of many years, there is no permanent pathological change in the joint or periarticular structure.

Intermittent hydrarthrosis is characterized by periodic attacks of effusion into one or more joints. There is usually a predilection for the larger joints, particularly the knee, although on occasions the hips, elbows and wrists may be involved. The attack lasts seven to ten days, subsides completely, and recurs in ten to twenty days. It is accompanied by pain, swelling, and stiffness of the joint, without redness. There is an accumulation of fluid in the joint space which may be seen on x-ray or with transillumination and may be aspirated. The periarticular structures are not involved. It frequently occurs in allergic individuals.

The method of study in suspected cases of allergic arthroses is directed toward the determination of the specific etiological factor. This is accomplished by a detailed history, physical examination, and laboratory studies to rule out nonallergic forms of arthritis. Allergy may be suspected if the symptoms occur in the presence of other allergic conditions and in an individual giving a positive family history of allergy. In such cases an allergic investigation may be of value in uncovering the specific allergens. The literature, however, cites many instances where clinical sensitivity to foods is found in patients with negative and variable skin reactions. In these cases the method of clinical or therapeutic trial may be resorted to.

The exact mechanism is unknown. Many cases may be explained on

an antigen-antibody reaction. Where specific allergens have not been determined, the underlying mechanism might be explained by some nonspecific stimulus such as those enumerated by Selye in the adaptation syndrome. The actual site of this reaction probably lies in the synovial membrane or endothelial lining of the small blood vessels.

SUMMARY

Three cases of allergic arthroses were presented, and the essential features were described. The reasoning for an underlying allergic hypothesis was discussed. These included the concomitant allergic findings in the patient, the positive family history for allergy, positive skin and passive transfer tests, blood eosinophilia, negative blood studies, sedimentation rate and x-ray findings. Relief of symptoms was obtained by placing the patient in the first case on an elimination diet. Both types of allergic arthritis appear to be distinct clinical entities. However, the offending allergen cannot be identified in all cases.

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REFERENCES

1. Berger, H.: Intermittent hydrarthrosis with an allergic basis. J.A.M.A., 112:2402, 1939.
2. Boemer, L. C.: Infection, arthritis and allergy with an allergic dietary regimen. Illinois M. J., 75:474, 1939.
3. Cain, J. C.: J.A.M.A., 125:1037, 1944.
4. Cain, J. C.: J.A.M.A., 125:1037, 1944.
5. Criep, L. H., Jr.: Bone & Joint Surg., 28:276, 1946.
6. Ferry, J. L.: Report of a case of palindromic rheumatism. J. Indiana M. A., 36:348, 1943.
7. Freund, E.: Gelenkerkrankungen. Vienna: Urban, 1929.
8. Grego, J. G., and Harkins, H. N.: Palindromic rheumatism. J. Michigan M. Soc., 43:401, 1944.
9. Hench, P. S., and Rosenberg, E. F.: Proc. Staff Meet., Mayo Clin., 116:808, 1941.
10. Hopkins, J. J., and Richmond, J. B.: Ann. Int. Med., 26:454, 1947.
11. Kahlmeter, G.: Acta med. Scandinav., 102:432, 1939.
12. Lewin, P., and Traub, S. J.: Allergic synovitis due to ingestion of English walnuts. J.A.M.A., 106:2144, 1936.
13. Mazer, M.: Palindromic rheumatism. J.A.M.A., 120:364, 1942.
14. Neligen, A. R.: Brit. M. J., 1:205, 1946.
15. Paul, W. D., and Logan, W. P.: Palindromic rheumatism. J. Iowa M. Soc., 34:101, 1944.
16. Paul, W. D., and Carr, T. L.: Arch. Phys. Med., 26:687, 1945.
17. Paul, W. D., and Logan, W. P.: Palindromic rheumatism. J. Iowa M. Soc., 34:101, 1944.
18. Perl, A. F.: Canad. M.A.J., 57:382, 1947.
19. Pottenger, R. T.: Constitutional factors in arthritis with special reference to incidence and role of allergic diseases. Ann. Int. Med., 12:323, 1938.
20. Service, W. C.: Hydroarthrosis of allergic origin. Am. J. Surg., 37:121, 1937.
21. Solis-Cohen, S.: On some angioneural arthroses commonly mistaken for gout and rheumatism. Tr. A. Am. Physicians, 28:739, 1913.
22. Solis-Cohen, S.: Am. J. M. Sc., 147:228, 1914.
23. Turnbull, J. A.: The relation of the anaphylactic disturbances to arthritis. J.A.M.A., 82:1757, 1924.
24. Vaughan, W. T.: Food allergy as possible factor in subacute recurrent arthritis. Ann. Int. Med., 19:122, 1943.
25. Wingfield, A.: Brit. M. J., 2:157, 1945.
26. Wolfson, S. A., and Alter, M. S.: Ann. Rheumat. Dis., 7:159, 1948.

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CLINICAL EXPERIENCES WITH B-(P-METHYLBENZHYDRYLOXY)-ETHYLDIMETHYLAMINE HYDROCHLORIDE

A New Antihistaminic

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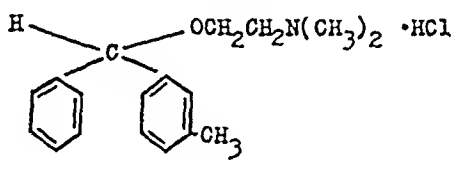
IN recent years many attempts have been made to produce drugs which would inhibit symptoms of allergy without the employment of specific pollen antigens. Since it is generally believed that at least some of the symptoms occurring in hay fever and other allergic diseases are due to the liberation of histamine or a histamine-like substance,[2,8] many chemical compounds have been synthesized in an attempt to block the action of histamine. Animal experimentation has shown that these drugs are powerful antagonists to many of the pharmacologic actions of histamine.[9,10,13,14] They appear to be effective in greatly diminishing or inhibiting the whealing phenomena of histamine, specific antigen reactions, and specific reactions in passively sensitized sites.[3,5] They seem to be of value in serum sickness, urticarial dermatoses, and in relieving the itching of various types of dermatitis.[1,4,6,7,11,12,15-18] Practically all the newer drugs that have shown any promise in the treatment of allergic diseases are those that are able to compete with histamine for attachment to the cell receptor, a phenomenon which is said to take place either by displacement or replacement of the histamine attachment by the drug.

It is the purpose of this paper to report the clinical antihistamine action of a new compound. This compound is chemically and pharmacologically closely related to Benadryl Hydrochloride, and in the laboratory appears to be more active than Benadryl. It is identified as B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride, whose structural formal is as follows:



MATERIAL AND METHOD

One hundred and thirty-five patients, 61 per cent females and 39 per cent males, whose ages ranged from fourteen to seventy-four, were included in this study. Patients were seen once a week and were required to give as accurate a description of daily symptoms as possible. Symptoms, dosage and side reactions were noted daily on cards provided for that

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B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride was supplied through the courtesy of Dr. E. A. Sharp, of Parke, Davis & Co., Detroit, Michigan.

TABLE I. TYPES OF ALLERGIC CONDITIONS IN ONE HUNDRED AND THIRTY-THREE PATIENTS

	No. Patients	Complete Relief No.	Complete Relief Per Cent	Partial Relief No.	Partial Relief Per Cent	Unimproved No.	Unimproved Per Cent	Total Relief No.	Total Relief Per Cent
Urticaria	8	6	75.0	2	25.0	0	0.0	8	100
Seasonal Allergic Rhinitis	79	17	21.5	52	65.8	10	12.7	69	87.3
Non-seasonal Allergic Rhinitis	36	9	25.0	19	52.8	8	22.2	28	77.8
Bronchial Asthma	12	0	0.0	5	41.7	7	58.3	5	41.7

purpose. Those patients who reported the most spectacular results were given placebo capsules for one to two weeks. The drug was administered in 25 mg. capsules four times daily. In only six cases was it necessary to reduce from 100 to 50 mg. daily. In two cases of bronchial asthma, in which symptoms seemed to be aggravated by the drug, it was necessary to discontinue the medication. During the ragweed season, particularly on days with high pollen counts, the dose was increased to 200 mg. without significant side effects but also without increased efficacy in relieving symptoms. Those patients who had at least 50 per cent relief of symptoms were considered improved and were classified as having obtained partial relief. Those patients who were classified as completely relieved had no symptoms at all. The results were evaluated according to the patients' own daily description, as well as the objective evaluation of the observer after repeated careful examination and inquiry.

Hyposensitization therapy with pollen and other inhalant extracts, as well as stock vaccine, were continued, and B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride was given as an adjuvant.

RESULTS

Urticaria.—Of the eight patients with urticaria, six suffered from simple urticaria, and two had urticaria and angioneurotic edema following the administration of penicillin. The six patients with acute urticaria reported complete relief after using the drug, while the two patients with angioneurotic edema had partial relief of symptoms with marked diminution of itching. Thus 100 per cent of the urticaria cases obtained satisfactory relief.

Seasonal Allergic Rhinitis.—This group consisted of patients with symptoms of nasal allergy due to pollen but also evoked as well by other inhalants, such as house dust, orris and animal danders. Of the seventy-nine patients, seventeen (21.5 per cent) reported complete relief from symptoms, fifty-two (65.8 per cent) had partial though satisfactory relief, and ten (12.7 per cent) were unrelieved. Sixty-nine (87.3 per cent) of this group reported satisfactory relief.

Nonseasonal Allergic Rhinitis.—There were thirty-six patients with perennial nasal allergy. Some of these patients showed positive skin reactions to inhalants and food extracts. In others, the allergic etiology was determined by environmental control or clinical trial. This group also

consisted of patients who gave negative skin reactions to the inhalants and foods, but who had infections of the nose or accessory nasal sinuses. All patients in this group had undergone specific hyposensitization therapy, nonspecific therapy of various types and trial with elimination diets, with little relief. Of the thirty-six patients taking the drug, nine (25 per cent), reported complete relief from symptoms, nineteen (52.8 per cent), had partial or satisfactory relief, while eight (22.2 per cent) were not helped at all. The latter eight patients all suffered from chronic upper respiratory infections. The total number of patients showing improvement was twenty-eight (77.8 per cent).

Bronchial Asthma.—Twelve patients suffering from bronchial asthma were given the new drug for symptomatic relief. Some experienced asthmatic symptoms as a result of a hypersensitiveness to inhalants, while others were infective or intrinsic in character. Of the twelve patients, none reported complete relief and five (41.7 per cent) had partial relief from their symptoms; seven (58.3 per cent), had no relief whatsoever. Two of the latter patients claimed that their condition was aggravated by the drug. Those who obtained no relief had upper or lower respiratory tract infections or both.

Side Effects.—Side effects occurred in twenty patients, as follows:

Drowsiness	12
Dizziness	3
Dryness of throat	2
Vomiting	2
Abdominal cramps	1

The drug was discontinued in two cases because of severe drowsiness. Generally speaking, there was evidence of central nervous system depression in those who reported side effects. Thus 15 per cent of the total group of 135 patients experienced side reactions of notable severity.

SUMMARY

B-(p-methylbenzhydryloxy)-ethyldimethylamine hydrochloride, a new antihistaminic, was administered to 135 patients with varied allergic manifestations. Of those with urticaria, 100 per cent were relieved; with seasonal allergic rhinitis, 87 per cent; with nonseasonal allergic rhinitis, 77 per cent; and with bronchial asthma, both seasonal and nonseasonal, 42 per cent. Side effects occurred in 15 per cent of the cases, and only two patients could not tolerate the drug. This new antihistaminic, with its minimum side effects, has proven a most potent adjuvant for relieving allergic symptoms when used with usual procedures in the therapy of allergy, such as elimination of allergens and hyposensitization. Further studies are now in progress to synthesize drugs of this nature with greater therapeutic value and possibly free from side reactions.

REFERENCES

1. Curtis, A. C., and Owens, B. B.: B-dimethylaminoethyl benzhydryl ether hydrochloride in treatment of acute and chronic urticaria. Univ. Michigan Hosp. Bull., 11:1, 1945.
2. Dale, H. H., and Laidlaw, P. P.: The physiological action of B-iminazolylethylamine. J. Physiol., 41:318, 1930.
3. Elias, H., and McGavack, T. H.: Influence of dimethylaminoethyl benzhydryl ether hydrochloride upon histamine flare reactions. Proc. Soc. Exper. Biol. & Med., 61:133, 1946.
4. Eyermann, C. H.: Clinical experiences with a new antihistaminic drug. J. Allergy, 17: 210, 1946.
5. Friedlaender, S., and Feinberg, S. M.: Histamine antagonist. III. The effect of oral and local use of B-dimethylaminoethyl benzhydryl ether hydrochloride on the wheaing due to histamine, antigen-antibody reactions, and other wheaing mechanisms; therepeutic results in allergic manifestations. J. Allergy, 17:129, 1946.
6. Friedlaender, A.: The use of a histamine antagonist. B-dimethylaminoethyl benzhydryl ether hydrochloride in allergic diseases. Am. J. M. Sc., (in press).
7. Levin, S. J.: B-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl), its use in allergic diseases. J. Allergy, 17:145, 1946.
8. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses. London: Shaw and Sons, Ltd., 1927.
9. Loew, E. R., Kaiser, M.E., and Moore, V.: Synthetic benzhydryl alkamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine. J. Pharmacol. & Exper. Therap., 83:120, 1945.
10. Loew, E. R., and Kaiser, M. E.: Alleviation of anaphylactic shock in guinea pigs with synthetic benzhydryl alkamine ethers. Proc. Soc. Exper. Biol. & Med., 58:235, 1945.
11. McGavack, T. H., Elias, H., and Boyd, L. J.: The influence of dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) upon normal persons and upon those suffering from disturbances of the autonomic nervous system. J. Lab. & Clin. Med., 31:560, 1946.
12. McGavack, T. H., Elias, H., and Boyd, L. J.: Some pharmacological and clinical experiences with Benadryl (dimethylaminoethyl benzhydryl ether hydrochloride). Am. J. M. Sc., (in press).
13. Mayer, R. L., Huttner, C. P., Scholz, C. R.: Antihistaminic and anaphylactic activity of some a-pyridinoethylenediamines. Science, 102:93, 1945.
14. Mayer, R. L.: Antihistaminic substances with special reference to pyribenzamine. J. Allergy, 17:153, 1946.
15. O'Leary, P. A., and Farber, E. M.: Benadryl in the treatment of urticaria. Proc. Staff Meet., Mayo Clin., 20:429, 1945.
16. Schwartz, E., and Levin, L.: Benzhydryl ether hydrochloride (Benadryl) in the symptomatic treatment of allergy. New York State J. Med., 46:1233, 1946.
17. Waldbott, G. L.: Clinical results with Benadryl. J. Allergy, 17:142, 1946.
18. Zolov, B.: Benadryl. J. Maine M. A., pp. 126-129, (May) 1946.

BRONCHIAL ASTHMA CAUSED BY THE INHALATION OF WOOD DUST

(Continued from Page 496)

7. Rosenbloom, J.: Report of a case showing the relation between occupation and a certain case of bronchial asthma. Am. J. M. Sc., 160:414, 1920.
8. Schonwald, P.: Cedar hay fever (Discussion of paper by J. H. Black). J. Allergy, 1:87, 1929.
9. Senear, F. E.: Dermatitis due to woods. J.A.M.A., 101:1527, 1933.
10. Stier, R. F. E.: Cedar hay fever (Discussion of paper by J. H. Black). J. Allergy, 1:88, 1929.
11. Walker, I. C.: Bronchial asthma. Oxford Med., 2:128, 1939. Quoted from Feinberg, S. M., Durham, O. C., and Dragstedt, C. A.: Allergy in Practice. Second ed. Chicago: Year Book Publishers, 1946.

PHENERGAN (R. P. 3277)

Preliminary Report of Clinical Effectiveness

MAURICE H. SHULMAN, M.D.
Boston, Massachusetts

IN an excellent article published in 1947, B. N. Halpern[2] described his studies of a new series of antihistaminic drugs. These were derivatives of thiodiphenylamine, and R. P. 3277 was listed as the most active of these derivatives. The report of complete animal studies, toxicology, and a bibliography are included in this monograph.[2]

An attempt to judge the clinical usefulness of this drug was begun with a small supply brought from France. A new technique for clinical evaluation of the efficacy of R. P. 3277, now known as Phenergan, had to be devised because the amount was limited. Large numbers of patients could not be tested. As a result, only those patients were selected in whom all other available antihistaminic drugs had given little or no relief.

The side effects of drowsiness and dizziness resulting from this drug were well known and reported by Halpern. He advised a single daily dose of 25 milligrams. In this study, patients were given this single dose immediately after the last meal of the day, thus diminishing the danger of toxic symptoms occurring during working and waking hours. Doses as low as 6.5 milligrams per day were frequently found sufficient. Such small doses often eliminated side effects which occurred with larger doses.

HAY FEVER

It is generally accepted that mild to moderate seasonal allergic rhinitis responds well to antihistaminic drug therapy. For this reason, seasonal allergic rhinitis was not included in this study.

BRONCHIAL ASTHMA

Asthma of all types responds poorly to antihistaminic therapy. This fact has been noted in nearly all clinical studies of such therapy. When improvement is noted in these cases, one must not lose sight of the beneficial effect of other medication employed, daily variation of symptoms, and sleep-producing side effects of the antihistaminic drug employed.

Only ten cases of asthma were selected as "failures." Each patient had been given various antihistaminic drugs with no amelioration of symptoms. Asthma was present continuously, varying only in intensity. Each person also had perennial vasomotor rhinitis. Of the ten patients given Phenergan, eight reported moderate to marked sleepiness. This occurred in spite of the single dosage system used. Seven patients reported good results, and three reported no improvement in symptoms.

For the purpose of this investigation it must suffice to say that seven

persons with asthma associated with allergic rhinitis reported improvement in their conditions after no results were noted with other antihistaminic drugs.

URTICARIA

Eight persons with severe generalized urticaria, which had persisted from two months to two years despite the use of various antihistaminic drugs, were given Phenergan. Two of these patients had been taking 400 milligrams of Pyribenzamine daily with no relief. All eight patients reported good to excellent results with Phenergan. One of the eight patients reported marked drowsiness.

In evaluating the efficacy of this drug in this selected group of eight cases of urticaria, it must not be overlooked that Phenergan was the only antihistaminic drug that afforded indisputable relief from symptoms.

PERENNIAL VASOMOTOR RHINITIS

In perennial vasomotor rhinitis many factors are operative, and the degree of the disease is ever changing. Symptoms in this condition may vary in intensity from hour to hour. Nevertheless, twenty cases of this type were found in which the common antihistaminics gave little or no relief. Phenergan was given once a day. Nine of these patients reported drowsiness. In one of these the disturbing degree of drowsiness necessitated the discontinuance of the drug. Only nine of the twenty patients reported good results with Phenergan.

ECZEMA

Antihistaminic therapy has been employed in cases of eczema with varying results.[3] Four cases of eczema were found for which various antihistaminic drugs had been prescribed with no relief of symptoms. One of the four patients reported toxic drowsiness after taking Phenergan but nevertheless continued to take the drug. Two of the four cases of eczema showed an improvement.

Separation of the side effects of drowsiness from the true antihistaminic action of this drug in these cases is almost impossible. It is only fair to say that a sound night's sleep with no scratching of the lesions may aid the healing of this condition as much as the therapeutic effect of the drug.

CONTACT DERMATITIS

Contact dermatitis is another condition which has been treated with antihistaminic drugs. Results have been equivocal. For this study, nine cases of contact dermatitis were selected. These patients had all been given many different antihistaminics to no avail. After taking Phenergan, one of the nine patients complained of dizziness and drowsiness while four reported drowsiness alone. Of the nine patients included in this group, only three patients reported good results.

The antipruritic effect of Phenergan is certainly as marked as any of the better known antihistaminics. The problem of the effect of sedation in contact dermatitis cannot be overlooked. As in eczema, improvement could conceivably be a result of sedation rather than antihistaminic action of the drug.

MIGRAINE

Migraine headache has responded poorly to antihistaminic therapy.[3] Four cases of migraine were selected which had received previous treatment with other antihistaminic drugs with little or no relief. These patients were instructed to take 25 milligrams of Phenergan as soon as prodromal symptoms appeared or at the onset of the headache. Of the four patients selected, two complained of slight drowsiness. In two patients results were good with an abrupt cessation of symptoms. The other two patients reported no results with this type of therapy.

DISCUSSION

Studies of toxicology or experimental animal work with Phenergan have been well done and reported in detail by B. N. Halpern[2] of France.

Our experience with Phenergan has been that the side effects occur with slightly greater frequency than with other antihistaminics. This finding has been corroborated by S. Feinberg.[1] The prolonged effect of this drug necessitates its administration once every twenty-four hours. By establishing a routine of taking the drug in the evening after supper, most of the unpleasant side effects are eliminated. Continued use of Phenergan has made patients less susceptible to these side effects. In no case was it necessary to increase the dosage of the drug even after prolonged administration and, for several of the cases, as little as 6.5 milligrams were sufficient for the alleviation of symptoms.

The clinical evaluation of the efficacy of any new drug presents inherent difficulties. There is no scientific yardstick for measuring subjective symptoms or improvement. "Good," "fair," and "poor" results are too dependent on the psychological make-up of the patient. Identical symptoms may cause extreme suffering in one patient and little or no discomfort in another. Normal daily variations in the intensity of symptoms in patients may be overlooked in the evaluation of any drug. The self-limiting character of many manifestations of allergy is another source of error in the attempt to determine results of treatment with any specific drug. Another source of error is the failure to consider the effect of other simultaneous treatment. With these pitfalls in mind, a definite idea of the value of Phenergan in various allergic syndromes, excluding hay fever, has been obtained.

SUMMARY

A limited supply of the drug necessitated the selection of cases unimproved by other antihistaminic drugs. Fifty-five patients who failed

to respond to commonly used antihistaminics were selected for trial with Phenergan. In this series twenty "failure" cases of perennial vasomotor rhinitis were given Phenergan. Only nine patients reported good results.

Ten "failure" cases with perennial and seasonal asthma were given Phenergan: seven patients reported marked improvement of symptoms and three reported no improvement.

Eight "failure" cases with urticaria were given Phenergan, and all patients reported excellent results..

Four "failure" cases of eczema were given Phenergan; two patients reported improvement and the other two reported no improvement.

Of the nine "failure" cases of contact dermatitis in this series, three patients reported good results and six had no results with Phenergan.

Of the four "failure" cases of migraine given Phenergan, two patients had good results and two had no results from this medication.

Of the fifty-five patients with various allergic conditions, except hay fever, comprising this study, all failed to respond favorably to the commonly employed antihistaminic drugs. These patients were placed on a new antihistaminic drug, Phenergan (R. P. 3277), which was given orally in a single daily dose ranging between 6.5 milligrams to 25 milligrams. Thirty-one (56 per cent) of these fifty-five patients showed marked improvement to complete relief of symptoms. Patients with urticaria, acute and chronic, showed the highest incidence (100 per cent) of excellent results. Our present results warrant further study of a larger group of allergic patients when Phenergan is readily obtainable.

I wish to express my appreciation to Dr. Murray Peshkin for his assistance in preparing this manuscript.

REFERENCES

1. Feinberg, S.: Personal communication.
2. Halpern, B. N.: Recherches sur une nouvelle serie chimique de corps doues de proprietes anti-histaminiques et anti-anaphylactiques les derives de la thiodiphenylamine. Arch. internat. de pharmacodyn. et de therap., 74:314-333, (June 15) 1947.
3. Waldbott, G. L., and Young, M. I.: Antistine, Neo-Antergan, Neohetramine, Trimeton, anti-histaminique R. P. 3277. An appraisal of their clinical value. J. Allergy, 19:313-316, (Sept.) 1948.

416 Marlborough Street

A few copies of *Psychodynamics and the Allergic Patient* by Harold A. Abramson, M.D., F.A.C.A., are still available. This little book of eighty-one pages represents a panel discussion on the subject at the third annual meeting of the College held at Atlantic City June 8, 1947. It is an official publication of the American College of Allergists, priced at $2.50. Orders should be placed directly with the Bruce Publishing Company, 2642 University Avenue, St. Paul 4, Minnesota.

THE ABSENCE OF THE EFFECTS OF BENADRYL ON THE HEMATOPOIETIC SYSTEM

HOWARD C. LEOPOLD, M.D., F.A.C.A.

Philadelphia, Pennsylvania

BENADRYL (Diphenhydramine hydrochloride) is one of the group of antihistaminic drugs which contain the benzene ring in their chemical structure. Drugs containing the benzene ring have produced damage to the blood-forming centers, with the subsequent production of anemia, leukopenia, neutropenia or thrombocytopenia. In 1946, because of the absence of reports on the effects of Benadryl on the hematopoietic system in humans, it seemed desirable to investigate this matter since this group of drugs was coming into increasing use.

A comprehensive review of the literature by Sachs[7] in 1948 listed numerous reports of the various effects of Benadryl other than effects on the hematopoietic system. The toxic reactions reported included neuro-psychiatric, alimentary, cardiovascular, respiratory, genito-urinary, muscular, ocular, and miscellaneous ones, but none involving the hematopoietic system. Blanton and Owens[2] reported a case of granulocytopenia, due possibly to Pyribenzamine. Crandall[3] reported that four or five patients who had received either Benadryl or Pyribenzamine in large doses for several months developed anemia with the red cell count down to 2.5 to 3 million, and the white cell count down to 1,200 to 1,500, with a decrease in granulocytes.

This study was initiated in 1946. The plan was to administer Benadryl to a small group of adult allergic patients in doses of 150 to 200 mg. daily over a long continued period of time. The patients, selected at random from the patients attending the Jefferson Hospital Allergy Clinic, had urticaria or asthma. The criteria of selection was that the patient had an allergic condition which might be benefited by the drug and which would require regular attendance at the clinic. Blood studies were performed prior to the initial dose of the drug and were repeated at weekly intervals. All blood counts were made at the same time of day, about 2:00 p.m. All the blood studies were performed by the personnel of the Charlotte, Drake, Cardeza Research Hematology Department of Jefferson Hospital.

Twelve patients comprised the initial group selected for the study. Two of the cases were dropped because of their inability to take the drug, manifested by severe nausea and vomiting or drowsiness. The patients were followed for an average of 9.9 months per patient. The actual period during which the patients were studied varied from a half year for six

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From the Allergy Clinic, Department of Medicine, Jefferson Medical College Hospital.

The Benadryl used in this study was supplied through the courtesy of Dr. E. A. Sharp of Parke, Davis and Company.

Read at the meeting of Philadelphia Allergy Society, October 27, 1948.

patients to over a year for four patients. Of the last group one patient was observed thirteen months, one patient for sixteen months, and two patients for seventeen months.

The blood counts included a red cell count, determination of the hemoglobin value in gm./100 c.c. and in percentage of normal, a total white cell count, a differential count, and a search for early forms. Bone marrow studies were to be done in any case presenting an abnormal blood count.

The administration of the drug produced no significant variation in the hemoglobin level or red cell content of the blood in any patient.

A knowledge of the normal values of the leukocytes in the blood is necessary to establish criteria for the diagnosis of leukopenia or neutropenia. The normal blood levels of leukocytes in adults are usually stated to range from 5,000 to 10,000 white blood cells per cu mm., as given by Wintrobe,[8] who states that "values below 5,000 indicate leukopenia." Gradwohl[1] states, "there are from 5,000 to 8,000 leukocytes per cu.mm. normally." The same author[4] states, "Neutrophiles comprise about 60 to 70 per cent of all leukocytes." But other authorities indicate that there are wider normal variations than have previously been recognized. As Beck[6] states, "Counts of from 3,130 to 13,680 have been reported on normal individuals; consequently one must know what is normal for a given individual before much can be said concerning a leukopenia or leukocytosis. The normals usually given (5,000 to 10,000) include only 90 per cent of healthy individuals." Osgood[7] states, "The total leukocyte count based on a study of 269 healthy adults of both sexes, nineteen years of age and over, has a range of 4,000 to 11,000 per cu. mm.," and that "segmented neutrophiles vary from 33 to 75 per cent (average 54 per cent) of the total number of white cells in the blood of adults of twenty years of age and over." Medlar[5] has stated, "There must occur a fluctuation of more than 50 per cent in the total count and of over 8 per cent in the differential picture before much significance can be placed on it." It is recognized that the normal white blood cell level varies with many factors, such as age and activity, and that an individual normal blood cell count must be established for each person. It is interesting to note that in this group of ten allergic individuals, four patients had an initial white cell count of 5,000 or less prior to the administration of the drug.

The standard accepted in this study for leukopenia was a white cell count below 3,000 cells/cu.mm., with a decrease of 50 per cent below the initial total white cell count. The standard for neutropenia was a neutrophile level below 50 per cent and a decrease of over 8 per cent of the differential picture. No patient, including those treated for over one year, developed leukopenia or neutropenia. No clinical purpuric or hemorrhagic manifestations occurred.

Observation for the presence of young cell forms was performed. Only in two cases, in single counts each, were metamyelocytes found. A

young lymphocyte was found in one case. In these three cases the above cells disappeared in later counts with continued administration of the drug. One patient had one normoblast and one erythroblast in a single count of twenty counts done; and in later counts, with continued administration of the drug, these cells were not present.

Eight of the ten cases had 10 to 17 per cent monocytes in a differential white count at some time during the study. In some patients, the high monocyte level was present in the initial count; in others, it occurred during the course of the study. There was no apparent relationship between the monocyte level and the continued administration of the drug. This high monocyte level was abnormal for published standards, as given by Wintrobe,[8] who states that the normal levels for monocytes are 3 to 7 per cent per cu.mm. Dr. Erf, of the staff of the Cardeza Research Hematology Department, informs me that the absolute number of monocytes found in these counts were within the usual range found in normal individuals by this laboratory. Perhaps allergy may be a possible cause of monocytosis.

Drug allergy has often occurred when a drug is readministered to a patient after an interval free of the drug. The course of events consists of a sensitizing dose of the drug, a free interval, and the administration of the shocking dose. In four of the patients, due to their failure to report regularly, free intervals occurred followed by the readministration of the drug. The free intervals varied from one to two weeks, with the exception of one case in which there was a free interval of three months. One patient revealed a progressive drop in total leukocytes, with no decrease in neutrophile percentage, when the drug was first administered, the total white count dropping from 5,350 to 3,300 cells per cu.mm. After a free interval of one week, the total white count was 5,000, and after two months of drug readministration the white count was 3,400, but the neutrophile percentage rose from 67 per cent to 73 per cent. The decrease in white cells occurred twice but the decrease was less than 50 per cent of the initial count and above the level for pathologic leukopenia, and neutropenia did not occur. In several patients similar temporary decreases in the white cell count were noted, followed by a return to the initial level or higher with continued administration of the drug. Readministration of the drug after a free interval in these cases did not produce anemia, neutropenia, leukopenia, or hemorrhagic phenomena.

SUMMARY

Benadryl, administered to patients for periods ranging from six months to seventeen months, did not produce any pathologic alteration in the hemoglobin, red cell, total white cell, or neutrophile content of the blood. No manifestations of purpura or hemorrhage occurred.

(Continued on Page 533)

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AMERICAN COLLEGE OF ALLERGISTS
FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

Under the Auspices of

Baylor University College of Medicine

Monday, October 31, through Saturday, November 5, 1949

DETAILED INFORMATION—REGISTRATION BLANK—
SCHEDULE OF FACULTY

The regular fall, intensive, graduate continuation course in allergy will be held at the Baylor University College of Medicine, Houston, Texas, commencing Monday, October 31, and extending to Saturday, November 5, inclusive.

Final registration will commence at 8:30 a.m., October 31. The daily hours of instruction will extend from 8:30 a.m. to 11:00 a.m. and from 1:15 p.m. to 5:00 p.m. Various lectures will be accompanied by graphic and clinical demonstrations, lantern slides, colored films, charts, et cetera. The Texas State Approval Agency for Veterans Education has approved this Course to train veterans under the provisions of Public Law 346, 78th Congress. The course includes all phases of the subject and will be presented by specialists in the fields of the basic sciences, as well as by specialists in allergy, who will deal with the treatment and management of the allergic patient. There will be two evening round-table discussions.

Make all requests for hotel accommodations directly with the Shamrock Hotel, attention of Mrs. Elsworth, Houston, Texas. In making your reservation, please state the exact time of your arrival and departure and whether you want a single room or wish to share one with another registrant. The number of single rooms is limited.

The fee for the Course is $100.00. Please make all inquiries and registrations for the Course directly with the Chairman, Dr. Homer E. Prince, Medical Arts Building, Houston, Texas. Members of the College, as well as candidates for Active and Associate Fellowships and non-members, are urged to register by mail before October 31.

REGISTRATION BLANK

To be completed and mailed to:

Office of the Chairman
Homer E. Prince, M.D.
Medical Arts Building
Houston, Texas

....
Date

(Type or Print).....
Last Name Initials

.....

.....
Street City Zone State

Check or Money Order Enclosed ☐
Will Remit at Time of Registration ☐
Member ☐
Non-Member ☐
Candidate ☐

THE AMERICAN COLLEGE OF ALLERGISTS

FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

Baylor University College of Medicine

Houston, Texas

October 31 — November 5, 1949

PROGRAM

MONDAY, OCTOBER 31, 1949

A.M.

8:30- 9:30 Registration

9:30- 9:45 Address of Welcome

DR. WARREN T. BROWN, M.D., Associate Dean, Professor of Psychiatry, and Chairman of the Department of Neuropsychiatry, Baylor University, College of Medicine, Houston, Texas.

9:45-10:15 The Field of Allergy (Orientation)

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts Medical School, Boston, Massachusetts.

10:15-11:00 Immunological Aspects of Allergy

FRED W. WITTICH, M.D., Secretary-Treasurer, The American College of Allergists, Minneapolis, Minnesota

P.M.

1:15- 2:00 Pharmacology of the Drugs used in Allergy

CHAUNCEY D. LEAKE, M.D., Executive Vice-President, University of Texas, Medical Branch, Galveston, Texas.

2:00- 3:00 The Physiology of Allergy

WILBUR A. SELLE, Ph.D., Professor of Physiology, University of Texas, Medical Branch; Consulting Physiologist, University of Texas Hospitals and the M. D. Anderson Hospital for Cancer Research, Galveston, Texas.

3:00- 3:30 History taking in Allergic Disease

WILLIAM L. MARR, M.D., Associate Professor of Internal Medicine, University of Texas, Medical Branch, Galveston, Texas

3:30- 4:00 The Treatment of Foreign Protein Reactions, especially to Penicillin, Insulin and Liver

ETHAN ALLEN BROWN, M.D., Lecturer in Allergy, Tufts Medical School, Boston, Massachusetts.

7:30 Dinner—Shamrock Hotel.

Address—A Modern Concept of Disease—JONATHAN TORMAN, M.D., President, The American College of Allergists, Columbus, Ohio.
Motion Pictures—HERBERT J. RINKEL, M.D.—Problems of the Allergic Patient.

TUESDAY, NOVEMBER 1, 1949

Respiratory Allergy

Asthma

A.M.

8:30- 915 *The Pathology of Asthma*

P. A. WHEELER, M.D., Assistant Professor of Pathology, Baylor University, College of Medicine, Houston, Texas.

9:15- 9:35 Physical Examination of the Chest in Asthma.

JAMES A. GREENE, M.D., Professor of Medicine and Chairman of the Department of Medicine, Baylor University, College of Medicine, Houston, Texas.

9:35-10:00 The Heart in Asthma.

EDGAR M. MCPEAK, M.D., Assistant Professor of Clinical Medicine, Baylor University, College of Medicine; Associate Physician in Medicine, Hermann Hospital, Houston, Texas.

10:00-10:30 Emphysema, Bronchiectasis and Asthmatic Bronchitis.

ALAN G. CAZORT, M.D., Assistant Professor of Medicine, Chief of Allergy Division, University of Arkansas, School of Medicine, Little Rock, Arkansas.

10:30-11:00 Bronchoscopic and Surgical Considerations of Some Pulmonary Conditions

HOWARD T. BARKLEY, M.D., Associate Professor of Clinical Surgery (Thoracic Surgery), Baylor University, College of Medicine, Houston, Texas.

P.M.

1:15- 2:15 Diagnosis, Management and Treatment of Asthma.

BOEN SWINNY, M.D., Civilian Expert to the Surgeon General and Consultant in Allergy, The Brooke General Hospital, San Antonio, Texas.

Hay Fever

2:15- 2:45 Physiology of the Upper Respiratory Tract

HERBERT H. HARRIS, M.D., Professor of Clinical Otolaryngology, Baylor University, College of Medicine: Chairman, Department of Otolaryngology, Jefferson Davis Hospital; Attending Surgeon, Department of Otolaryngology, Hermann Hospital, Houston, Texas.

2:45- 4:00 Hay fever—Symptoms, Diagnosis and Management

FRENCH K. HANSEL, M.D., Director, The Hansel Foundation; Editor-in-Chief, Annals of Allergy, St. Louis, Missouri.

4:00- 5:00 *The Relationship of the Paranasal Sinuses to Bronchial Asthma*

J. MATHEWS ROBISON, M.D., Professor and Chairman of Department of Otolaryngology, Medical Branch, University of Texas, Galveston, Texas; Associate Professor of Clinical Otolaryngology, Baylor University, College of Medicine, Houston, Texas.

7:30 Informal discussion groups by various members of the faculty and demonstration by representatives of pharmaceutical companies to be held at the Shamrock Hotel.

WEDNESDAY, NOVEMBER 2, 1949

A.M.

8:30- 9:30 The Specific Diagnosis of Respiratory Allergic Disease

HERBERT J. RINKEL, M.D., Kansas City, Missouri.

9:30-11:00 The Specific Treatment of Respiratory Allergic Disease

BOEN SWINNY, M.D., Civilian Expert to the Surgeon General and Consultant in Allergy, The Brooke General Hospital, San Antonio, Texas.

P.M.

1:15- 2:00 Gastrointestinal Allergy, Including Chronic Ulcerative Colitis

ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, San Francisco; Allergist, Samuel Merrit Hospital, Oakland; Allergist, Cowell Infirmary, University of California, Berkeley; Allergist, United States Naval Hospital, Oakland, California.

2:00- 2:40 Allergic Headaches

ORVAL R. WITHERS, M.D., Associate Professor of Medicine, University of Kansas Medical School; Chief, Allergy Clinic, Out Patient Department, University of Kansas Hospital, Kansas City, Missouri.

2:40- 3:00 Desensitization to Foods

J. H. BLACK, M.D., Professor of Clinical Medicine, Southwestern Medical College, Dallas, Texas.

3:00- 4:30 Elimination Diets in the Diagnosis and Treatment of Clinical Food Allergy.

ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, San Francisco; Allergist, Samuel Merrit Hospital, Oakland; Allergist, Cowell Infirmary, University of California, Berkeley; Allergist, United States Naval Hospital, Oakland, California.

4:30- 5:00 Drug Allergies

WILLIAM H. BROWNING, M.D., Shreveport, Louisiana.

7:30 Informal discussion groups by various members of the faculty and demonstrations by representatives of pharmaceutical companies to be held at the Shamrock Hotel

THURSDAY, NOVEMBER 3, 1949

Dermatologic Allergy

A.M.

8:30- 9:00 Atopic Dermatitis from the Allergist's Viewpoint

J. H. BLACK, M.D., Professor of Clinical Medicine, Southwestern Medical College, Dallas, Texas.

9:00- 9:15 Atopic Dermatitis—Dermatological Treatment

WILLIAM A. SMITH, M.D., Beaumont, Texas.

9:15- 9:45 The Id Reaction

C. M. GRISWOLD, M.D., Past Professor of Dermatology and Syphilology, Baylor University, College of Medicine, Houston, Texas.

9:45-10:30 Contact Dermatitis

WILLIAM A. SMITH, M.D., Beaumont, Texas.

10:30-11:00 Urticaria

D. H. HOTCHKISS, M.D., Associate Professor of Clinical Medicine, Baylor University, College of Medicine; Consultant, Internal Medicine, Veterans Administration Hospital, Houston, Texas.

Allergens

P.M.

1:15- 2:15 Botanical Factors

HERBERT J. RINKEL, M.D., Kansas City, Missouri.

2:15- 2:45 Miscellaneous Inhalant Factors

ALAN G. CAZORT, M.D., Assistant Professor of Medicine, Chief of Allergy Division, University of Arkansas, School of Medicine, Little Rock, Arkansas.

2:45- 3:15 Fungous Factors

HOMER E. PRINCE, M.D., Associate Professor of Medicine, Baylor University, College of Medicine; Chief, Allergy Service, Hermann Hospital, Houston, Texas.

3:15- 3:45 Foods and Drugs

ORVAL R. WITHERS, M.D., Associate Professor of Medicine, University of Kansas Medical School; Chief, Allergy Clinic, Out Patient Department, University of Kansas Hospital, Kansas City, Missouri.

3:45- 5:00 Preparation and Standardization of Extracts

WILLIAM H. BROWNING, M.D., Shreveport, Louisiana.

FRIDAY, NOVEMBER 4, 1949

Role of Infection and Bacterial Allergy in Asthma

A.M.

8:30- 9:00 Diagnosis: History, Physical Findings and Laboratory Procedures
L. O. DUTTON, M.D., El Paso, Texas.

9:00- 9:30 Treatment: Removal of Foci, the Use of Antibiotics and Vaccines.
L. O. DUTTON, M.D., El Paso, Texas.

9:30-10:15 Psychosomatic Problems in Allergy
HAL M. DAVISON, M.D., Chief in Medicine, Georgia Baptist Hospital, Atlanta, Georgia.

10:15-10:40 Ocular Allergy
HUGH KUHN, M.D., Chief of Staff, Kuhn Clinic Hospital, Hammond, Indiana.

10:40-11:00 Aural Allergy
HUGH KUHN, M.D., Chief of Staff, Kuhn Clinic Hospital, Hammond, Indiana.

Pediatric Allergy

P.M.

1:15- 2:00 Eczema and Urticaria in Infants and Children.
ALBERT V. STOESSER, M.D., Clinical Professor of Pediatrics, University of Minnesota Medical School; Chief of Allergy Clinics, Minneapolis General Hospital and University Hospital, Minneapolis, Minnesota.

2:00- 2:45 Gastrointestinal Allergies of Infants and Children
WALTER L. RUCKS, M.D., Associate Professor of Pediatrics, University of Tennessee Medical School; Chief of the Department of Pediatrics, Baptist Hospital, Memphis, Tennessee.

2:45- 3:30 Perennial Rhinitis and Asthma
ALBERT V. STOESSER, M.D., Clinical Professor of Pediatrics, University of Minnesota Medical School; Chief of Allergy Clinics, Minneapolis General Hospital and University Hospital, Minneapolis, Minnesota.

3:30- 4:15 Preventive Allergy
ORVAL R. WITHERS, M.D., Associate Professor of Medicine, University of Kansas Medical School; Chief, Allergy Clinic, Out Patient Department, University of Kansas Hospital, Kansas City, Missouri.

4:15- 5:00 Practical Allergy Management in Pediatrics
WALTER L. RUCKS, M.D., Associate Professor of Pediatrics, University of Tennessee Medical School; Chief, Department of Pediatrics, Baptist Hospital, Memphis, Tennessee.

6:00 Cocktail hour—Grecian Room, Shamrock Hotel.

SATURDAY, NOVEMBER 5, 1949

Veterans Bureau Hospital

A.M.

8:30- 9:15 Office Management and Economic Problems in Allergy

JOHN D. GILLASPIE, M.D., Boulder, Colorado.

9:15-10:00 Practical Handling of the Allergic Patient

HAL M. DAVISON, M.D., Chief in Medicine, Georgia Baptist Hospital, Atlanta, Georgia.

10:00-10:30 Physical Allergy

CECIL M. KOHN, M.D., Chief of Department of Allergy, Kansas City General Hospital, Kansas City, Missouri.

10:30- 1:00 Practical Demonstrations.

(a) Vegetation Dermatitis

HUGH GRAHAM, M.S., Director of Graham Laboratories, Dallas, Texas.
WILLIAM A. SMITH, M.D., Beaumont, Texas.

(b) Skin Testing

PAUL T. PETIT, M.D., Beaumont, Texas.
ALAN G. CAZORT, M.D., Assistant Professor of Medicine, Chief of Allergy Division, University of Arkansas, School of Medicine, Little Rock, Arkansas.
D. H. HOTCHKISS, M.D., Associate Professor of Clinical Medicine, Baylor University, College of Medicine; Consultant, Internal Medicine, Veterans Administration Hospital, Houston, Texas.

(c) Ophthalmic Testing

JOHN D. GILLASPIE, M.D., Boulder, Colorado.

ORVAL R. WITHERS, M.D., Associate Professor of Medicine, University of Kansas Medical School; Chief, Allergy Clinic, Out Patient Department, University of Kansas Hospital, Kansas City, Missouri.

(d) Air Analysis by Slide and Plate Methods

J. M. ROSE, M.D., Houston, Texas.

(e) Cytological and Bacteriological Examinations

FRENCH K. HANSEL, M.D., Director, The Hansel Foundation: Editor-in-Chief, Annals of Allergy, St. Louis, Missouri.

L. O. DUTTON, M.D., El Paso, Texas.
WILLIAM L. MARR, M.D., Associate Professor of Internal Medicine, University of Texas, Medical Branch, Galveston, Texas.

(f) Circulation Time.

WILLIAM H. BROWNING, M.D., Shreveport, Louisiana.

Luncheon.

Questions and Answers.

MICROPOWDERED AMINOPHYLLINE OR THEOPHYLLINE INHALATION THERAPY IN CHRONIC BRONCHIAL ASTHMA

Evaluation by Recorded Vital Capacity Changes

GEORGE V. TAPLIN, M.D., ARTHUR L. GROPPER, M.D., and GORDON SCOTT
With the technical assistance of
JAMES R. HAGEMAN
Los Angeles, California

PRELIMINARY investigations early in 1947 with the inhalation of micropowdered mixtures of Benadryl and glucose, alone or combined with various vasoconstrictors such as Propadrine or Neo-Synephrine, have been reported in part elsewhere.[12] In May and June, 1947, ten cases were studied, and relatively crude micropowdered aminophylline-glucose preparations were used. The clinical and vital capacity results were encouraging. At this time Barach[2] had already reported that inhalation of nebulized aminophylline solutions was of clinical benefit. Later Prigal et al[10] reported improvement in 80 per cent of forty patients similarly treated. Both investigators used 0.25 to 0.5 gram doses of aminophylline. Because of the high local concentrations obtained by inhalation procedures, it was thought that much smaller amounts might be as effective and safer for preliminary clinical trials. Therefore, in all initial studies, preparations were made containing therapeutic agents in approximately one-tenth the standard oral or intravenous dose. Since Mayer et al[9] had shown that inhalation of 2 per cent Pyribenzamine as an aerosol was effective in preventing histamine anaphylaxis in guinea pigs, 1 per cent amounts by weight were selected for use with various powdered antihistamines, such as Benadryl, Bromothen and Chlorothen. In general, our subsequent studies have substantiated these original principles of dosage. Feinberg[4] has shown in animal experiments that inhaled aerosols of numerous antihistamines in 0.25 to 2.0 per cent concentrations are effective in much smaller amounts than the dosage required by injection.

Because of recent increasing interest in the value of inhaling various drugs as aerosols, it was decided to make a more complete study and evaluation of inhaled xanthines as micropowders. The advantages of using fine powders by inhalation have been reported previously.[6,13] In this investigation an attempt has been made to find an inhalation dosage effective for the average asthmatic, the duration of action of inhaled xanthines, and the place for this form of inhalation therapy in the symptomatic treatment of chronic bronchial asthma.

From the Investigative Medicine Service, Birmingham General Hospital, Van Nuys, California, and the Department of Medicine at the University of California School of Medicine at Los Angeles.
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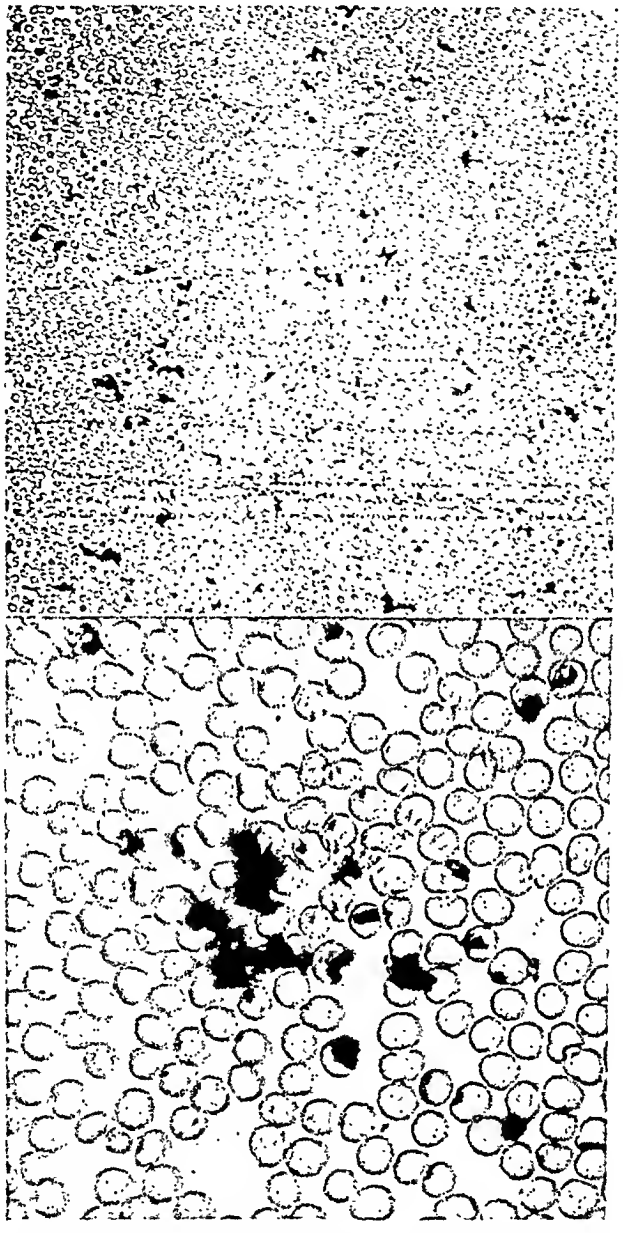
Dr. Taplin is an associate clinical professor of medicine, University of California School of Medicine at Los Angeles.
Dr. Gropper is, at present, an intern in medicine, University of Rochester School of Medicine, Rochester, New York.
Mr. Scott is, at present, a medical student at the University of Southern California, Los Angeles.

Aerosol Inhalation Therapy and Importance of Particle Size.—According to many investigators,[1,3,5,7,11,14] dusts or mists must be administered in a finely-divided state to obtain complete pulmonary penetration. Most



Figs. 1 and 2. Photomicrographs demonstrating particle size of aminophylline micropowders compared with human red blood cells. (Fig. 1) Magnification 100x. (Fig. 2) Magnification 400x.

nebulizers advocated for use with penicillin and epinephrine solutions produce particles which range from 0.5 to 5 microns in diameter. More than 97 per cent of the dose inhaled is retained in the respiratory tract with such aerosols. With this particle size range, less is lost by impingement in the mouth and pharynx, and more remains to penetrate deeply into

the bronchial tree. When large particle size preparations are inhaled, more than 50 per cent may be impinged on the throat and subsequently swallowed. Similar principles apply to the administration of particulate aerosols.

The aminophylline preparations used in this study, generously supplied by G. D. Searle and Co., were pulverized to a particle size with individual particles 2 microns in diameter or less. Theophylline-lactose preparations were produced and freely supplied by the Lederle Laboratories Division of the American Cyanamid Company. However, since the aminophylline preparations were associated with relatively large agglomerates of small particles (Figs. 1 and 2), it was necessary to devise methods of dispersing agglomerates. It was found that relatively finely-pulverized lactose acted as a dispersing agent by reducing electrostatic effects, and also aided in disguising the bitter taste and slightly ammoniacal odor of aminophylline. The dispersed mixtures were prepared by adding the aminophylline and lactose powders in equal parts by volume.

The amount of agglomeration has been reduced further by minor modifications in the inhalator used to administer these preparations.

Inhalator Apparatuses Used.—Initial studies with aminophylline-theophylline preparations were undertaken using the insufflator type of apparatus previously described[12] because it produced a finer suspension of particles than the smaller inhalator. Later it was discovered that the inhalator used for penicillin micropowers* was efficient if the calibre of the delivery tube was increased to provide for greater ease of inhalation and if a fine mesh screen or other suitable device was placed over the base of the outlet tube to prevent the passage of large agglomerates (Fig. 3). These modifications are of benefit even when non-agglomerated micropowders are used, because they provide for easier administration and slower velocity of powder delivery. The latter feature results in reduced impingement of the powder on the pharynx and thereby increases the amount of drug reaching the bronchial tree.

Studies on Dosage by Inhalation.—Pilot studies in six cases indicated that doses varying between 60 and 240 mg. made little difference in the degree of immediate response as measured by vital capacity recordings. Although many patients have obtained relief with approximately as little as 5 to 15 mg., a standard dose of 60 mg. of aminophylline or theophylline, made up in a lactose-dulcin-vanillin vehicle, was adopted for this study. Subsequent observations throughout the period of this experiment have indicated that this dose is satisfactory in mild and moderate cases, but frequently the same dose given repeatedly may be required in severe asthmatic states.

*The original inhalators (trade mark "Penlators") were produced and supplied by the Lederle Laboratories Division of the American Cyanamid Company for the administration of micropowdered penicillin.

Procedures and Apparatuses for Recording Vital Capacity.—In the first experiments a Benedict-Roth basal metabolism apparatus was used as a spirometer, and vital capacity recordings were not made. Generally, a prolonged expiration time was observed. This was estimated at first

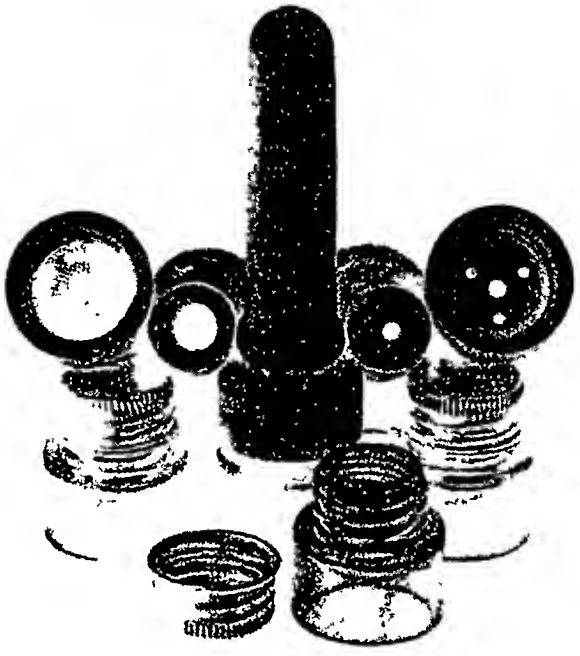


Fig. 3. The modified inhalator apparatus (left) compared with the original, showing the 70-mesh screen inserted at the base and the increase in calibre of the outlet tube. The hermetically-sealed cartridges (powder chamber of the apparatus) are shown attached and detached from the inhalators.

by the use of a stopwatch. Later, in order to make permanent records, the same metabolism apparatus was used with its rotating drum attached. Normal tidal air changes and maximum inspiration and expiration volumes were recorded. It was apparent that if the records were spread by increasing the velocity of the kymograph, more detailed information could be obtained regarding expiration rates. Therefore, a drum with three times the diameter of the original was substituted. Subsequent records were made using this modification of the apparatus. Later, the procedure was further simplified without loss of important information by having patients record maximum expirations only. Patients preferred this procedure since it required less effort and caused less discomfort, particularly when repeated determinations were made at frequent intervals before and following inhalations of sugar placebos or aminophylline-theophylline preparations. It was found that this procedure, if repeated too frequently, caused a reduction in vital capacity by itself. Therefore, it was necessary to vary the intervals between tests according to each patient's reaction to the procedure. In general, ten- to 15-minute intervals

were found satisfactory. A more detailed discussion of this vital capacity recording procedure, using a more accurate instrument, is to be the subject of a separate report.

METHODS OF STUDY

Of thirty-five patients investigated, thirty were hospitalized cases at the Birmingham Veterans Administration Hospital. These individuals were mainly veterans of World War I and had been studied and hospitalized periodically for the past five to thirty years. All had been investigated completely from the general medical, bacteriological and allergic aspects of their problems. All of the patients had chronic bronchial asthma, and they ordinarily required or obtained frequent and varied kinds of asthmatic therapy, including injections of epinephrine, aminophylline and parenteral fluids, aminophylline suppositories, hyposensitization, iodides by mouth, sedation, and inhalation of 1:100 nebulized epinephrine.

Consideration of Psychogenic Factors.—These inhalation experiments with micropowdered aminophylline-theophylline preparations were undertaken with full knowledge of the psychological effects of a new procedure on this group of patients. As was expected, there was an initial wave of enthusiasm which subsided after two cases successfully treated had been discharged and two other patients had reverted to status asthmaticus while under this form of therapy. Because of the well-known psychosomatic factors in many patients with asthma,[16] it was considered necessary to make as many control observations and objective measurements as possible to avoid erroneous interpretations.

Validity of Recorded Vital Capacity Measurements.—In order to determine the significance of vital capacity measurements in asthmatics, it was necessary to make numerous determinations on normal persons as well as the cases studied. Forty normal patients were able to duplicate their vital capacity records with a variation of not more than 200 c.c. Except in severe asthmatics and in a few individuals who were not particularly cooperative, this range of accuracy could be obtained. Vital capacity records were considered valid when values were duplicated within this range of variation.

It was soon discovered that there was a measurable relation between the severity of asthmatic symptoms and variations in vital capacity. There was also a relation between emotional factors and reduced lung volume. These lung capacity changes were found to occur with extreme rapidity and with surprising magnitude (400 to 800 c.c.) in several patients. It was noted that cough associated with expectoration was frequently followed by a rise in vital capacity of as much as 200 to 400 c.c. On the other hand, a paroxysm of dry coughing generally produced an immediate reduction in lung capacity of as much as 200 to 800 c.c.

Coughing was found to be more frequent when the pretreatment lung capacity was below 2500 c.c. and less frequent when at levels of 3000 c.c. or above. In these cases there seemed to be a correlation between the degree of bronchiolar spasm and irritability of the cough reflex. There is little doubt, after several hundred vital capacity determinations, that the procedure itself, especially when performed during severe or moderately severe asthmatic states, reduces the duration of relief which usually follows inhalation of micropowdered xanthines. This undesirable effect may be prevented by requiring such cases to perform the test less frequently.

Inhalation of Powdered Placebos.—To insure that aminophylline inhalations did not alter vital capacity by suggestion, each patient was tested at least once, and many patients several times, using inhalations of flavored sugar in the same manner that aminophylline preparations were studied. This control procedure was of considerable value, since in nearly all patients, with the exception of a few who had copious expectoration after the sugar inhalation, there was no significant increase in vital capacity. Although some patients, particularly during mild asthmatic states, were not able to distiguish the placebo from the therapeutic inhalation and obtained subjective improvement, most patients with moderate or severe asthma could readily make this distinction.

Spontaneous Vital Capacity Variations in Asthmatics.—Another feature of importance in evaluating the symptomatic effectiveness and duration of action of therapeutic agents in asthma is the recognition of a normal daily variation in vital capacity. This variation was found to correlate closely with the patients' statements that they were worse in the morning, better during the day, and frequently more asthmatic in the evening or at specific intervals during the night. Therefore, ten of these patients' vital capacity changes were measured at various times during the day and evening. Measurements performed only in the morning, when vital capacity is usually increasing spontaneously, may give erroneous results, especially regarding duration of drug action. Numerous recorded vital capacity tracings demonstrate that ten patients responding well during the early morning likewise obtain benefit during the evening. Fortunately, the usual vital capacity response to inhaled aminophylline is almost immediate. The maximum rise in nearly all patients occurs within five to fifteen minutes. Vital capacity increases of less than 200 c.c. in relation to control values are considered insignificant.

Induced Vital Capacity Changes During Attacks of Asthma.—By recording vital capacity changes while patients are becoming asthmatic spontaneously, one can estimate the clinical effectiveness of inhalation therapy objectively. In general, the immediate rise of vital capacity is satisfac-

TABLE I. CLINCIAL RESPONSE TO INHALED XANTHINE MICROPOWDERS IN RELATION TO DEGREE OF ASTHMATIC SEVERITY

Case No.	Initials	Age	Severe (V.C. 2000 c.c. or less)		Moderately Severe (V.C. 2000-3000 c.c.)		Mild (V.C. 3000 c.c. or more)	
			Subjective Response	Vit. Cap. Response	Subjective Response	Vit. Cap. Response	Subjective Response	Vit. Cap. Response
1	F.N.	56	Good	Good*	Good	Good*	Good	Good*
2	G.E.T.	26	Good	Good	Good	Good	Good	Good
3	H.C.	55	Poor	Poor	Fair	Fair	Fair	Fair
4	H.D.	60	—	N.R.	Fair	Fair	Fair	Fair
5	E.R.	61	—	N.R.	Good	Fair	Good	N.R.
6	E.K.	29	—	N.R.	Good	N.R.	Good	Good
7	C.L.	36	Fair	Good	Good	Good	Good	Good
8	C.L.A.	51	Good	Good	Good	Good	Good	Good
9	P.D.R.	42	Good	Good	Good	Good	Good	Good
10	J.R.	48	Good	N.R.	Good	Good	Good	Good
11	W.B.	51	Good	Good	Good	Good	Good	Good
12	E.D.	60	Good	Good	Good	Good	Good	Good
13	J.J.Y.	27	Good	Good	Good	Good	Good	Good
14	K.R.	57	Good	N.R.	Good	Good	Good	Good
15	T.F.	63	Good	Fair	Good	Fair	Good	N.R.
16	E.R.	30	Good	Fair	Good	Fair	Good	Fair
17	M.E.	63	Good	Good	Good	Good	Good	N.R.
18	R.P.	60	Good	Good	Good	Good	Good	N.R.
19	G.H.	35	Good	N.R.	Good	Good	Good	Good
20	C.E.	43	Good	N.R.	Good	Good	Good	Good
21	A.N.	64	Good	Good	Good	Good	Good	N.R.
22	J.M.D.	52	Good	Good	Good	Good	Good	Good
23	J.S.	40	—	N.R.	Good	Good	—	N.R.
24	H.N.	48	—	N.R.	Fair	Fair	Good	N.R.
25	B.H.	52	Good	N.R.	Good	Good	Good	N.R.
26	R.B.J.	53	—	N.R.	Good	Good	Good	N.R.
27	W.H.S.	50	Good	Good	Good	Good	Good	Good
28	W.G.	30	—	N.R.	Good	Good	Good	Good
29	D.R.D.	50	Good	N.R.	Good	N.R.	Good	N.R.
30	A.R.L.	40	—	N.R.	Fair	Good	—	N.R.
31	P.H.F.	60	Good	Good	Good	Good	Good	N.R.
32	J.B.A.	49	Good	N.R.	Good	Good	Good	N.R.
33	E.R.	64	Good	N.R.	Good	Good	Good	N.R.
34	B.J.B.	54	Good	Good	Good	Good	Good	Good
35	J.H.	32	Good	N.R.	Good	Good	Good	Good

*Good: Symptomatic relief, associated with vital capacity rise of 400 c.c. or more.
Fair: Some relief, associated with vital capacity rise of 200-400 c.c.
Poor: Little relief, associated with vital capacity rise of 200 c.c. or less.
N.R.: Vital capacity changes not recorded.

tory, but the duration of response is short, varying between twenty and forty minutes in severe asthmatic attacks, lasting as long as one to three hours in moderately severe states, and for three to eight hours in mild states of asthma. These statements are based on an analysis of the recorded measurements in eighteen severe cases, thirty-three moderately severe and twenty-one mild cases (Table I).

Induced Vital Capacity Changes Following Intravenous Injections of Aminophylline.—Twelve of these asthmatic patients have been studied in a similar manner after administering aminophylline intravenously, using standard doses of 240 mg. in most cases and 480 mg. in a few. Nine patients obtained subjective relief within five to fifteen minutes. However, maximum increases in vital capacity did not appear in five instances until fifteen to thirty minutes later. This is a slower response than that following aminophylline or theophylline inhalation. Seven of these twelve patients stated that the intravenous mode of administration gave a more complete relief, especially during severe phases of asthma. However, in

five of these seven cases there was little difference in the maximum vital capacity response between the two modes of administration. There are four plausible reasons for this disparity: (1) when patients become panicky during a severe attack, they may be unable to self-administer the powdered preparation effectively, mainly because of their greatly increased residual air; (2) the duration and degree of action of the intravenously administered aminophylline appears to be slightly longer and greater; (3) most of these people have become conditioned over a period of many years to the benefits of injection treatments; and (4) the inhalation procedure requires more effort on the part of the patient than the passive receipt of an injection.

CLINICAL RESULTS AND COMMENTS

As a result of studying thirty-five cases of chronic bronchial asthma over a period of six months, during which interval many of these patients were treated on an ambulatory as well has hospital status, it was found that thirty of thirty-five patients obtained good symptomatic relief (Table I). It was possible to study many of these patients during asthmatic states of all degrees of severity. The recorded response to inhaled xanthines is variable from time to time, even in the same individual. Many severe attacks were relieved and more were aborted. Also, numerous moderate attacks were completely relieved which otherwise would have required injection therapy of some kind. Nearly all patients have obtained symptomatic relief during mild states of asthma. Several patients have become dependent to a large extent on this form of inhalation therapy. Four patients were followed who have used micropowdered aminophylline inhalations continuously for a period of five to six months. They used 60 mg. doses three to eight times daily, and little objective or clinical evidence of the development of tolerance to inhaled aminophylline has been observed.

Most patients can be taught to self-administer the preparations effectively during the first few doses. Mild coughing frequently occurs with the initial treatments, but most patients find satisfactory means of modifying the inhalation procedure to avoid this reaction. The inhalation procedure requires one to five minutes for the majority of patients.

OBJECTIVE RESULTS

From the data presented in Figure 4, the inhalation of 60 mg. of micropulverized aminophylline produces an immediate significant rise in vital capacity which averages 555 c.c., or a 21 per cent increase compared with the average pretreatment value recorded in these patients. The results were computed from 152 recorded vital capacity test series performed in duplicate or triplicate at frequent intervals during the first hour after the drug was inhaled.

Figure 4 also presents the response to inhaled theophylline in the same

dosage, computed from twenty-six similar test series, and shows an average rise of 583 c.c. or a 22.8 per cent increase over the control values.

Inhaled placebos of the flavored lactose base used in the xanthine preparations produce an insignificant change in vital capacity. Forty-one

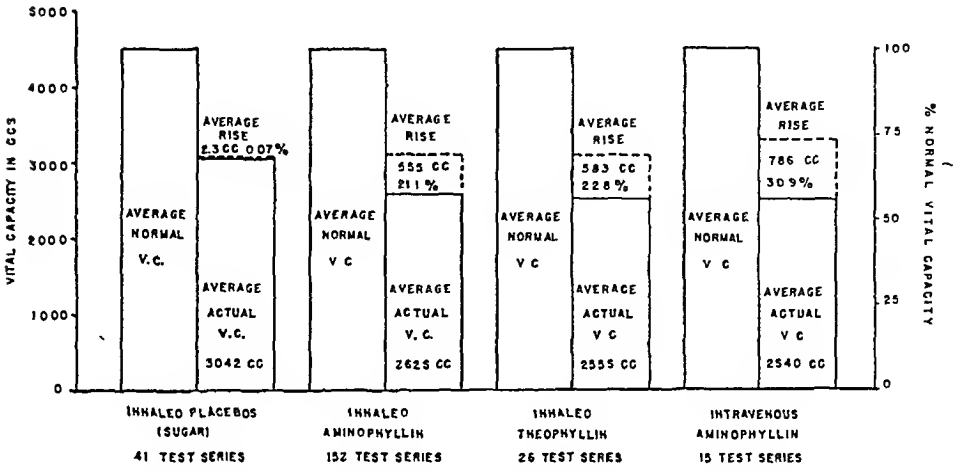


Fig. 4. Average vital capacity response to inhaled micropowders compared with intravenous aminophylline. The average values shown were computed from maximum vital capacity responses recorded in duplicate or triplicate from series determinations made at frequent intervals during the first hour after treatment. Sixty mg. doses of aminophylline and theophylline were used most frequently by inhalation, whereas 240 to 480 mg. doses of aminophylline were given by intravenous injection.

test series were performed and the results computed in a similar manner. Most of these tests were performed while the subjects were only moderately or mildly asthmatic. This choice was made because with this degree of severity the test procedure was better tolerated and the results were more reliable. Several patients were unable to distinguish between placebos and subsequent aminophylline therapy.

The average rise in recorded vital capacity measurements after injecting 240 or 480 mg. of aminophylline intravenously was 786 c.c. or 30.9 per cent over the control value. This is four to eight times the average dose used by inhalation, and the response is only about 30 per cent better than that which follows the inhalation procedure.

The maximum vital capacity response after inhaling 60 mg. of micropowdered aminophylline, in relation to the severity of the asthmatic state, is recorded in Figure 5. The objective findings confirm the clinical responses obtained. Although the average rise in vital capacity is quite similar in all degrees of asthmatic severity, the percentage rise compared with the pretreatment control value is greatest in the severe states and least in mild asthmatic states. Similar increments over pretreatment values of vital capacity are associated with greater symptomatic relief in severe asthma than when the condition is mild.

DISCUSSION

Probable Mode of Action of Inhaled Micropowdered Xanthines.—The rapidity of the response to inhaled xanthines and the relatively small dosage required probably indicates a local release of bronchiolar muscle

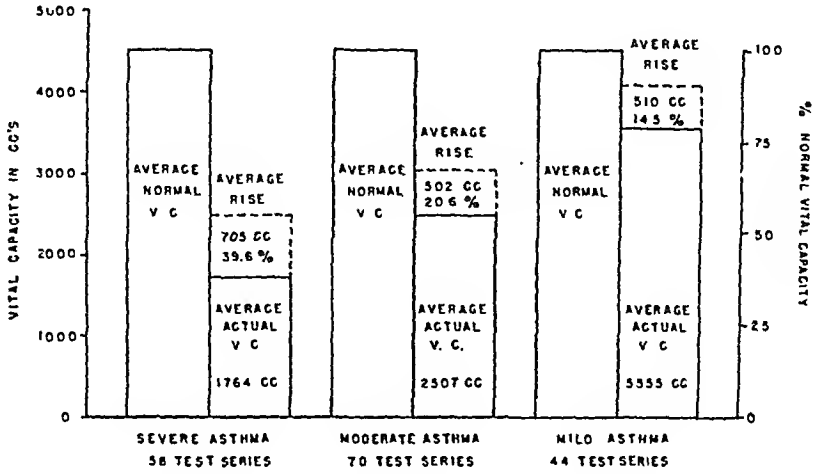


Fig. 5. Maximum vital capacity response to inhaled micropowdered aminophylline during the first hour after treatment in asthma. The data were computed as in Figure 4 to compare the responses following inhaled aminophylline in relation to the severity of the asthmatic state.

spasm. No attempt has been made to determine blood concentrations[15] or urinary excretion because present chemical methods are not sufficiently sensitive to measure the low concentrations likely to be present following such small doses.

Reactions to Inhaled Xanthines.—This method of administration has been unusually free of important reactions of any kind. No physical signs of allergic or local irritative respiratory effects were observed. No detectable changes in the lung field have been noted by fluoroscopy or in roentgenograms of the chest. There have been no systemic vasomotor reactions of the type sometimes observed when aminophylline is administered too rapidly by intravenous injection.[8,18]

Disadvantages in the Use of Inhaled Xanthines by this Method.—Frequently patients in status asthmaticus have difficulty in self-administering the micropowdered preparations efficiently, due to their greatly reduced vital capacity and associated panic states. Some patients complain of the somewhat bitter taste and ammoniacal odor. A few individuals, particularly those of highly nervous temperament, complain that the preparations produce persistent coughing which makes this form of therapy unsatisfactory for them.

It is important that the micropowders be prepared, packaged, and administered in a completely dry state. Otherwise the beneficial results are impaired and the preparations deteriorate too rapidly.

It has been suggested that the lactose vehicle used in these preparations may cause the deterioration and discoloration of aminophylline. We are investigating various other vehicles which do not contain an aldehyde group, the chemical group responsible in part for the above deterioration.[17] The moisture content of the powders should be kept below 0.1 per cent. Greater water content brings about similar changes.

SUMMARY

Inhalation of particulate xanthine aerosols has been shown to be an effective form of symptomatic therapy in thirty of thirty-five cases of chronic asthma. The relief is rapid and satisfactory in most mild and moderate cases. In severe attacks the duration of relief is usually short (twenty to forty minutes). In severe episodes, repeated doses have maintained satisfactory control in numerous instances and have prolonged the interval between required injections. This method of administration is of particular usefulness in the symptomatic treatment of ambulatory chronic asthmatics and is free of important side reactions. Overdosage is seldom encountered because the effective dose by inhalation is relatively small.

The clinical response and symptomatic relief obtained from inhaled micropowdered xanthines has been evaluated primarily on the basis of objective measurements. The important psychogenic factors have been reduced to a minimum by the control measures employed during the investigations.

ACKNOWLEDGMENTS

We wish to thank the Lederle Laboratories Division of the American Cyanamid Company for a grant-in-aid and for supplying theophylline and the inhalators (trade mark "Penlators").

We are also grateful to G. D. Searle and Company for providing a grant-in-aid and for supplying the micropulverized aminophylline.

REFERENCES

1. Abramson, H. A.: Principles and practice of aerosol therapy of lungs and bronchi. Ann. Allergy, 4:440, 1946.
2. Barach, A. L.: Treatment of intractable asthma. J. Allergy, 17:352, 1946.
3. Barach, A.: Inhalation treatment of bronchial asthma. New York State J. Med., 46:1002, 1946.
4. Feinberg, S. M.; Noren, B., and Feinberg, R. M.: Histamine antagonists. XI. Aerosolized antihistamine drugs in the prevention of histamine bronchospasm in guinea pigs. J. Allergy, 19:90-99, 1948.
5. Heubner, Wolfgang: Uber Inhalation. Zerstaubter Flussigkeiten. Ztsch. f. d. ges. exper. Med., 10:269-333, (Nov.) 1919.
6. Krasno, L.; Karp, M., and Rhodes, P. S.: Inhalation of penicillin dust. Science, 106:249, (Sept. 12) 1947.
7. Krueger, A., et al: Am. J. M. Sc., 206:40, 1944.
8. Lee, D. J.: Allergy in pediatrics. Clin. Proc. Children's Hosp., Washington, D. C., 2:133, 1946.
9. Mayer, D. L.; Brousseau, D., and Eisman, P. D.: Pyribenzamine aerosol inhalation and its influence on histamine poisoning and anaphylaxis. Proc. Soc. Exper. Biol. & Med., 64:92, 1947.

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ALLERGY OF THE EYE ASSOCIATED WITH MIGRAINE HEADACHE

Case Report

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THE patient was a young male student, aged twenty-two, who was referred for complaints of migraine-like headaches, and because the examining opthalmologist found the fields of vision in both eyes to be markedly contracted for both white and color vision. The history was that of headaches and flashes of light, starting seven weeks previously and accompanied on several occasions by nausea and vomiting. The headaches, which were formerly unilateral on right side, were present on both sides at the time the patient was seen. They were described by patient as not being severe but persisting even during sleep.

An effort to elicit any personal or familial history of allergy at first failed. It was discovered several months later, however, that there were several cases of eczema and asthma on the mother's side of the family tree, extending back three and four generations. The mother had eczema as a child and one brother had a suspicious "allergic" winter cough.

The patient's habits were moderate; he smoked one to two packages of cigarettes daily and drank about five cups of coffee. He had suffered from enuresis during childhood and otherwise had usual childhood diseases. He was in the Army Air Corps for twenty-one months and was discharged in perfect health except for a bullet wound in the right arm which left him with some stiffness of elbow.

The general physical examination revealed a well-nourished young man, with normal heart and lungs and a blood pressure of 110/70. There was some congestion of nasal turbinates and a mucoid nasal discharge. The Wassermann test and complete blood count, as well as a urinalysis, were normal. The fundus and visual fields examination, as done by Dr. Alice Deutsch, was as follows: "Mild photophobia, mild congestion of conjunctiva; both eye balls were pale; the pupils were equal, round and reacted well to light and accommodation; motility normal. Fundus (dilated pupils) media clear, disk normal; considerable mottling of the fundus periphery especially in the region of the equator. This mottling is the same in both eyes. The right eye, also, shows several irregularly outlined old choroiditic patches in the inferior nasal quadrant. These patches are surrounded and covered with the coarse pigment particles, as seen after disturbances in circulation in the posterior ciliary arteries. Visual fields for white, red and blue vision are markedly contracted, as shown in Figure 1.

$$\text{Vision: O.D.} = -.50 = \frac{20}{25} \quad \text{O.S.} = -.50 = \frac{20}{25}$$

The scratch tests were done and showed doubtful reactions to a few foods and inhalants. Intradermal tests, however, gave large reactions to canteloupe and tomatoes, and smaller but definite reactions to pork, lamb, milk, orange, wheat, and grapefruit. The patient was put on a trial elimination diet and told to avoid the foods mentioned above. Inasmuch as he showed a 2-plus reaction to tobacco, he was advised to cease smoking during this trial period.

The patient reported back two weeks later, stating that he had been completely free of headaches while on this diet. He was told to add pork to his diet, since his eating habits had changed while being away from home, and he was eating much pork. One week later, he reported back, stating that the pork caused a return of severe headache. He was then advised to leave foods containing pork completely out of his diet, and add wheat instead. The following week he reported back to state that he

had no further headaches and felt well The visual fields at this time were markedly improved, as shown in Figure 2

At weekly intervals one food was added at a time to his diet, viz, orange juice, grapefruit, cooked tomatoes, raisins, and finally canteloupe Over a period of four

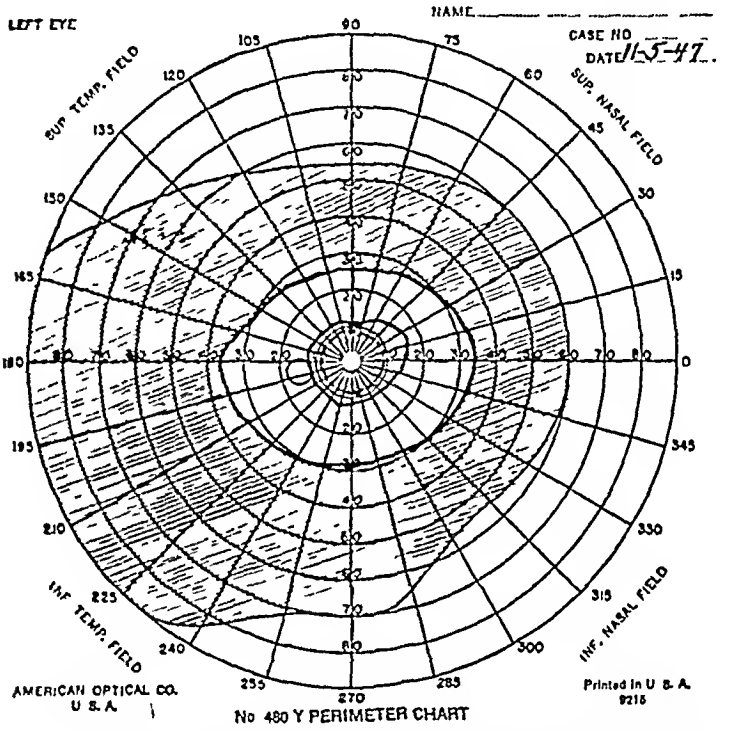

Fig 1 Marked contraction of the visual fields The shaded area is for white vision The inner circles are for blue and red vision, respectively The visual fields in the right eye are substantially the same as in the left eye, shown in Figures 1, 2 and 3.

months this patient continued to feel well and free of any complaints A re-check of his visual fields at this time revealed almost complete return to normal for form (white vision), as shown in Figure 3 The peripheral field for red and blue were still contracted but showed marked improvement The central vision was unchanged.

DISCUSSION

Ever since 1930 when Coca[3] reported a case of localized retinal edema in a patient thought to be sensitive to foods, there have been numerous cases of ocular allergy noted. In 1937, Plumer[7] reported a case of sudden loss of vision, with congestion and haziness of the left macula, apparently due to allergy to foods and inhalant substances. Allergic reactions of the retina in two patients were described by Bedell.[1] There were edema of the disks and areas of edema of varying prominence and size in the retina. It has been known for a long time that ocular allergy frequently is a manifestation of serum sickness. In 1925, Brown[2] reported the ocular reactions in seventy-five patients who received diphtheria antitoxin intravenously.

Lacrimation and dilatation of the conjunctival vessels occurred frequently. The retinal veins and capillaries were dilated, and definite papilledema developed in 20 per cent of cases. There was also a "watered silk" appearance of the retina in the patient with the severer reactions. About 10

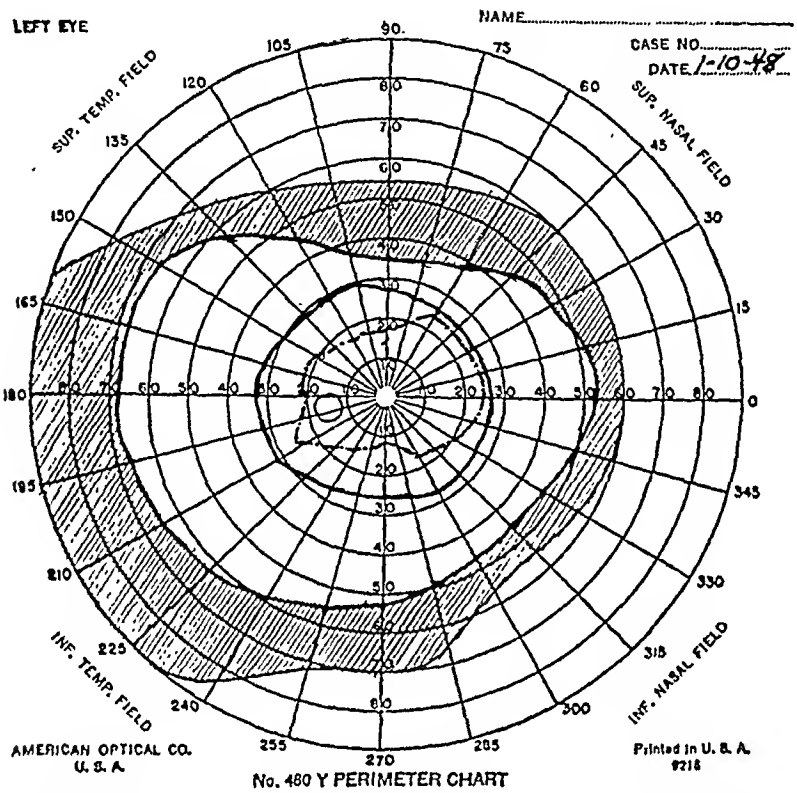

Figure 2. Marked improvement in visual fields, along with relief of migraine.

per cent of the patients complained of "blurriness" of vision which was temporarily relieved by epinephrine.

Although the headaches described in our case were not considered as typical migraine, it was felt that the association of migraine-like headaches with retinochoroideal abnormalities was more likely to prove to be on an allergic basis. The first series of migraine cases thoroughly investigated by allergic methods was presented by Vaughan[8] in 1927. In an analysis of thirty-three patients with migraine, allergy to foods was shown to play a definite part in twelve. Since Vaughan's original report, numerous presentations have been made in support of the thesis that allergy is an important factor in migraine. Whereas foods are the usual causes of allergic migraine, it should be remembered that almost any allergen is capable of producing symptoms. Drugs have been known to cause migraine. Injected substances may also cause allergic headaches, as well as other types of allergic reactions. Goltman[6] reported instances of migraine in which inhalants, such as animal danders, pollen and orris root, were the main

etiological factors. Feinberg[5] has also corroborated the occasional role of inhalant allergens in this syndrome.

Duggan[4] believes that the basic pathology in ocular allergy is a problem in vascular physiology. He states "The basic pathologic process of the

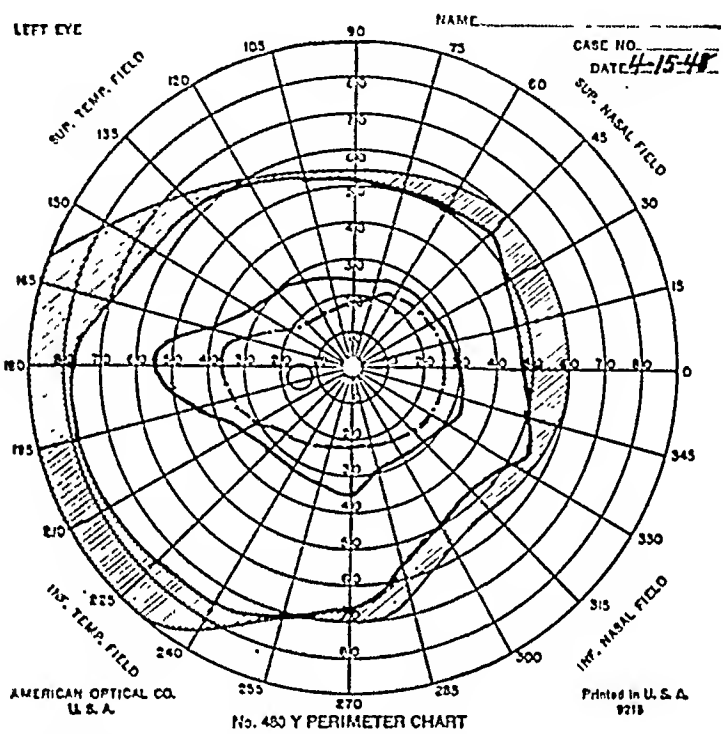

Fig. 3. Almost complete return to normal of the visual fields, with no further migraine. The inner circles represent the peripheral fields for blue and red vision, which show marked improvement.

lesions in allergy can be interpreted as a manifestation of arteriolar spasm or increased capillary permeability or both. Moreover, all chemical, nervous or other agents which can cause either arteriolar spasms or increased capillary permeability or both must be regarded as direct or contributing causes of allergy."

CONCLUSION

Therefore, it must be supposed that the primary lesion in this case was not in the vessels of the retina but in arteriolar spasm of the blood vessels which nourish the choroid and the adjoining retinal structures, resulting in the fundus changes described above. Although retinal edema seems to be the usual picture seen in this type of ocular allergy, there is probably another variant of this. The pathology in migraine has also been attributed by many authors to a localized area of edema in the brain, associated with vascular spasm and dilatation. Vaughan,[8] in 1927, stated, "There is con-

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CUTANEOUS REACTIONS TO TOBACCO ANTIGEN IN ALLERGIC AND NONALLERGIC CHILDREN

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THE incidence and specificity of the cutaneous reactions obtained with tobacco antigen, as well as the importance to be attributed to this substance in the pathogenesis of certain vascular diseases, continue to be the subject of controversial discussions.

The great divergence in the results obtained by different authors that have studied this problem in children[1,3] gave rise to this work, which was planned with two goals: (1) to verify the incidence of positive intradermal reactions to tobacco in both allergic and nonallergic children; (2) to determine the immunologic significance of such reactions.

MATERIAL AND METHOD

Two hundred nonallergic male children, from five to thirteen years of age, and 200 allergic children of both sexes, from two to thirteen years of age, constituted the material for this investigation. Among the allergic children, fifty had mothers who had used tobacco during the whole period of gestation and lactation. Of the 150 remaining children, only their fathers were smokers. It was not possible to obtain data in this sense concerning the children of the normal group because they were interned in an educational institution, away from their parents.

Among the allergic children, all with a history of atopy, 140 suffered from asthma and coryza, forty from rhinitis and twenty from eczema. Most of them presented positive intradermal tests to inhalants allergens, excluding pollens and molds.

The extract employed in all this work was obtained from cured leaves of six different species of tobacco (Burley, Maryland, Xanthis, Virginia, Havana and Baiano). The dust* obtained from the separate trituration of the leaves was mixed equal parts and treated exhaustively with anhydric ether until complete discoloration occurred. The resulting material was saturated with a buffered saline solution containing 1 per cent of sodium formaldehyde sulfoxylate, and placed in the refrigerator under toluol for forty-eight hours. After this time the extract was filtered, dialyzed for thirty days in cellophane 1,200, freed from toluol and sterilized by Seitz filtration. The final extract was adjusted to pH 7 and standardized by determination of its protein nitrogen (0.09 mg. NP/c.c.). Every three months a new extract was prepared. All of the extracts used showed a high degree of potency in the intradermal tests in persons with tobacco sensitivity.

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*The microscopic examination of the tobacco leaf powder did not reveal the presence of pollen grains. In some cases its culture showed the presence of cladosporium.

All children were submitted to intradermal tests by injecting 0.01 to 0.02 c.c. of the extract into the external surfaces of their upper arms. The reactions were read at the end of fifteen minutes and classified according to Cooke's suggestion.[2]

From children with doubtful or positive reactions, blood was taken for a search for reagins. Two-tenths c.c. of the undiluted serum of each child was injected into the skin of three different subjects, the same tobacco extract being used to test the receptors at the end of forty-eight hours. The reactions obtained in the passive transfer sites were classified as in the direct intradermal tests. Attempts to exhaust the passive sensitized sites of the receptors were made with the same tobacco extract, by intradermal injections of 0.05 c.c. every forty-eight hours. In order to study the specificity of the reagins for tobacco allergen and the existence of cross-reactions with other allergens to which the children were already sensitized, the same tobacco-sensitized sites of the receptors were tested and exhausted with extracts of house dust, wool, kapok, feathers, *C. dactylon*, ragweed and cladosporium.

COMMENTS

The analysis of the tables here presented show that our findings are nearer to those obtained by Peshkin and Landay[3] than to those mentioned by Chobot.[1] The incidence of positive reactions in 200 nonallergic children (7.5 per cent) was less than that for allergic children (17.5 per cent). Age and sex did not appear to be of importance in these results. Attention is called to the highest percentage of positive reactions (30 per cent) found among the fifty children descended from mothers who used tobacco during the whole period of gestation and lactation, as compared to that of 150 children (13.4 per cent) whose fathers alone were smokers. The results suggest sensitization *in utero* or by way of maternal milk, since sensitization exclusively by way of tobacco smoke would not explain satisfactorily such a great difference. Unfortunately, it was not possible to obtain data concerning the nature of any contacts that the children of the nonallergic group might have had with tobacco during their infancy or childhood. The predisposition of allergic children to acquire sensitivity seems to explain why they had a higher incidence of positive reactions.

Three-plus reactions were encountered among normal children (two cases) as well as among allergic children (five cases), but none of them presented constitutional reactions. The specificity of the reactions, 1+, 2+ and 3+, could be ascertained by the studies using the transfer tests. We were able to find reagins to tobacco in six of fifteen nonallergic children whose reactions were 1+ (two cases), 2+ (two cases) and 3+ (two cases). In the seven children showing plus-minus reactions, the search for reagins were always negative. In the thirty-five allergic children having direct positive tests, we found reagins in fifteen, among

TABLE I. SUMMARY OF THE TOTAL PERCENTAGE OF REACTORS AND THE DEGREE OF REACTIONS IN 200 ALLERGIC AND 200 NONALLERGIC CHILDREN, INTRADERMALLY TESTED WITH TOBACCO EXTRACT

Children	Reactions to Intradermal Injection of 0.01-0.02/c.c. of the Extract Containing 0.09 mg.NP per c.c.							
	Negative			Positive				
	Total	Per Cent	±	+	++	+++	Total	Per Cent
200 Nonallergic	185	92.5	7	4	2	2	15	7.5
200 Allergic	165	82.5	15	10	5	5	35	17.5

TABLE II. CORRELATION BETWEEN THE DEGREE OF REACTION AND THE INCIDENCE OF REAGINS TO TOBACCO AMONG THE ALLERGIC AND THE NONALLERGIC CHILDREN

Degree of Reaction to Intradermal Tests	Nonallergic Children		Allergic Children	
	No.	With Reagins	No.	With Reagins
±	7	0	15	0
+	4	2	10	6
++	2	2	5	4
+++	2	2	5	5

TABLE III. DEGREE AND TOTAL PERCENTAGE OF REACTION AMONG THE ALLERGIC CHILDREN WHO HAVE HAD DIFFERENT CONTACT WITH TOBACCO

Smoker	No. of Children	Intradermal Reactions to 0.01-0.02/c.c. of the Extract					
		±	+	++	+++	Total	Per Cent
Father and Mother	50	6	4	3	2	15	30
Father	150	9	6	2	3	20	13.4

which there were six with 1+, four with 2+ and five with 3+ reaction. In this group also the search for reagins in patients having plus-minus reactions was negative.

The specificity of the reagins to tobacco allergen in our material and the nonexistence of cross-reactions between this allergen and the allergens of pollens (grass and ragweed) could be clearly demonstrated by passive transfer studies. None of the other allergens to which the children were already sensitized were capable of exhausting or neutralizing the tobacco reagins found in the fifteen allergic and in the six nonallergic children.

SUMMARY

1. The results of intradermal tests performed with tobacco leaf extract in 200 allergic and 200 nonallergic children showed that this antigen is not a primary irritant.

2. The cutaneous reactions obtained with this extract were shown to be definitely specific and mediated by reagins:

3. Of the 200 allergic children, thirty-five (17.5 per cent) gave positive reactions, and reagins were found in fifteen. Among the 200 nonallergic children, fifteen (7.5 per cent) gave positive reactions, and reagins were found in six.

4. The incidence of positive reactions was greater among children whose mothers used tobacco during the whole period of gestation and lactation.

REFERENCES

1. Chobot, R.: The significance of tobacco reaction in allergic children. J. Allergy, 6:383, 1934.
2. Cooke, R. A.: The treatment of hay fever by active immunization. Laryngoscope, 25:108, 1915.
3. Peshkin, M. M., and Landay, L. H.: Cutaneous reactions to tobacco antigen in allergic and nonallergic children. Am. J. Dis. Child., 57:1288, 1939.

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ALLERGY OF THE EYE ASSOCIATED WITH MIGRAINE HEADACHE

(Continued from Page 527)

siderable evidence that in migraine a central nervous system angiospasm exists. Angiospasm is the characteristic vascular phenomenon in anaphylaxis."

The role which the tobacco played in our case can therefore be interpreted as a chemical agent which, by its well-known vasospastic action, can act as a contributing cause of ocular allergy. The combination, therefore, of a primary migraine due to foods and a secondary spastic agent explains the clinical picture thus described. We believe, therefore, that this is an unusual case of ocular allergy, wherein the picture of localized retinal edema was absent and was overshadowed by the picture of mottling and pigmentation of the fundus periphery, together with marked contraction of the visual fields.

The above case was seen through the courtesy of Dr. Louis Levy.

REFERENCES

1. Bedell, A. J.: Stereoscopic fundus photography. J.A.M.A., 105:1502, 1935.
2. Brown, A. L.: Am. J. Ophth., 8:614, 1925.
3. Coca, Arthur F.: Specific sensitiveness as a cause of localized retinal edema. Bull. New York Acad. Med., 6:593, 1930.
4. Duggan, W. F.: Vascular basis of allergy of the eye. Arch. Ophth., 36:551, 1946.
5. Feinberg, S. M.: Allergy in Practice. Pp. 733-741. Chicago: Year Book Publishers, 1946.
6. Goltman, A. M.: The mechanism of migraine. J. Allergy, 7:351, 1936.
7. Plumer, J. S.: Retinal allergy, case report. Arch. Ophth., 17:516, 1937.

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A HANDY DROPPER FOR SCRATCH TESTING

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THE use of scratch testing in the practice of allergy is practically universal, and the methods and materials used have become quite standardized. We are reporting a simple method which we have found useful in handling the allergic extracts used in scratch testing.

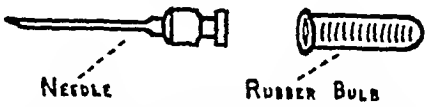

Fig. 1. The separate components of the dropper. When the rubber bulb is mounted on the hub of the needle, the useful dropper is formed.

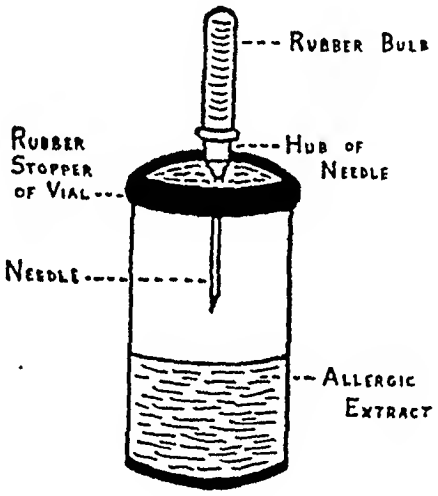

Fig. 2. The dropper in place in a vial of allergic extract. The vial is tilted so that the needle strikes the extract; then, by compressing the bulb, several drops of extract can be taken up. The dropper is removed from vial, and the allergic extract is dropped on the skin for testing.

Originally this method was improvised as a necessity. A shipment of our allergic extracts for scratch testing arrived in rubber-stoppered vials without glass droppers or glass rods, and we were faced with the problem of getting a drop of the extract each time for skin testing, without making up a new set of dropper bottles or taking off the tops of the vials and using toothpicks to get a drop of extract, or using similar improvised measures. The method which we finally devised has never been reported to our knowledge, yet it is simple, efficient and economical.

The materials used consist of a hypodermic needle and a rubber bulb. The needles can be any size within the range of about 1 inch length and

19 to 21 gauge. These needles can be salvaged from used ones too old and dull for intravenous use. The rubber bulbs are obtained from the small droppers which are put into the containers with liquid vitamin samples or with 1:100 epinephrine solution or with some nose drops. Any pharmacy, if notified, can accumulate large numbers of these rubber bulbs in a short time. The needles and rubber bulbs are washed and sterilized and are then ready for use. One needle and one bulb is needed for each vial of extract. It should be emphasized that the smaller sized bulbs are needed to make the fitting air tight. The large bulbs from the usual type of eye dropper are too large to fit tightly on the needle hub.

The rubber bulbs, when attached to the hubs of the needles (Figs. 1 and 2), make useful droppers which can be pushed through the rubber stoppers of the vials of allergic extract and can take up drops of the extract, which can then be transferred to the abraded skin for testing. When not in use, the needles are pushed all the way into the tops of the vials, thus maintaining their sterility; yet they are always ready for instant use.

This method avoids the necessity of special dropper bottles; it prevents spilling of allergic extracts if the vials are accidentally tipped, and it maintains sterility. The droppers are easily made, and they utilize waste materials which are generally found in any hospital or clinic.

THE ABSENCE OF THE EFFECTS OF BENADRYL ON THE HEMATOPOIETIC SYSTEM

(Continued from Page 512)

Readministration of the drug after a free interval did not produce any significant change in the blood picture.

REFERENCES

1. Beck, R. G.: Laboratory Manual of Hematological Technic. P. 79. Philadelphia: W. B. Saunders Co., 1938.
2. Blanton, W. B., and Owens, M. E. B., Jr.: Granulocytopenia due probably to Pyribenzamine. J.A.M.A., 134:454, (May 31) 1947.
3. Crandall, F. J., Jr.: Letters Internat. Correspondence Soc. Allergists, 11:2, 1947.
4. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis. Vol. I, pp. 496 and 555, fourth edition. St. Louis: C. V. Mosby, 1948.
5. Medlar, E. M.: Arch. Int. Med., 57:367-378, 1936.
6. Osgood, E. E.: Laboratory Diagnosis. Pp. 231-233, third edition. Garden City: Blakiston Co., 1940.
7. Sachs, B. A.: The toxicity of Benadryl: report of a case and review of the literature. Ann. Int. Med., 29:135-144, (July) 1948.
8. Wintrobe, M. M.: Clinical Hematology. Second edition, page 159. Philadelphia: Lea and Febiger, 1947.

235 S. 15th Street

MANAGEMENT OF ANESTHESIA FOR THE ALLERGIC PATIENT

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Reading, Pennsylvania

A SURVEY of literature and case reports suggests that people suffering from some allergic condition are more susceptible to reaction from anesthetic agents and drugs. Before any patient is subjected to anesthesia, therefore, it is important that a strict preoperative regime be followed. (1) The anesthetist should visit the patient. This should be done (a) in order to perform a satisfactory physical examination, (b) to obtain an adequate history, and (c) to attempt to allay fear of the operation. (2) It is well to consult laboratory reports. (3) Conferences should be held with the surgeon in order to obtain any vital information that he may have to offer. We will not go into detail concerning the above at this time, but will be content to say that, by following the routine outlined, the anesthetist will obtain much information which will be helpful to him in selecting the proper medication, anesthetic agent, and technique.

With this procedure, the anesthetist may discover positive indication of allergy. Should this be so, the patient should then be prepared properly, preferably by a consulting allergist. The allergic condition should be controlled as much as possible, particularly if the respiratory system is involved. It is not amiss, if desirable and possible, to postpone the operation. Proper premedication must be selected. An attempt should also be made to alleviate any fear of operation that the patient may have.

For the purpose of discussion, allergy may be divided into two parts: (1) allergy in clinical practice; (2) allergy in association with drugs and agents used in connection with anesthesia. Knowledge of the former may be obtained by following the preoperative routine mentioned above. The main interest lies in lesions of the skin and involvement of the respiratory system. Complications involving other organs of the body must not be overlooked and must be dealt with accordingly.

If the skin is involved at the proposed site of puncture, skin lesions would contraindicate the use of local, regional, or spinal anesthesia, eliminating possibility of any secondary infection. With this exception, patients with such a pathologic condition will tolerate any anesthesia. One should be certain, however, that the allergic skin condition is not due to some drug or agent that is about to be used for premedication or the anesthetic procedure.

Local or topical application of drugs to involved mucous membranes of the nose and throat will increase edema, swelling, and secretion. If a vasoconstrictor is added to the anesthetic solution, the action may be favorable. Irritating general anesthetic agents, such as ether and vineth-

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ene, add insult to injury by increasing the mucosal secretions. Agents which cause little or no irritation to the mucous membranes are more advantageous. Among these may be listed avertin, pentothal sodium, cyclopropane, nitrous oxide, ethylene, or combined anesthesia. By combined anesthesia is meant a combination of agents containing a minimum of each. Because of the site of the operative field, it may become necessary to employ an endotracheal catheter through which the inhalation agent may be administered. By so doing, the anesthetist will be out of the way of the surgeon. Local, regional, and spinal anesthesia may be used if applicable.

The asthmatic patient presents the greatest problem because of difficulty in breathing, increased pulmonary secretions, edema, and congestion. It is important that these persons be well oxygenated and hyperventilated at all times, especially while under the influence of general anesthesia with depressed respiration. This is also important during the inhalation of anesthetic mixtures which, being heavier than air, cause still more difficulty in breathing because of slower diffusion. Endotracheal intubation and positive pressure will be helpful in preventing anoxic anoxia. The endotracheal catheter in place is also of value as an avenue for passing an endotracheal suction catheter to withdraw excess secretions. Local, regional, or low spinal anesthesia may be used to great advantage in such persons. High spinal anesthesia, however, for upper abdominal surgery causes further respiratory depression and increased hypoxia. The patient will be in greater distress. Postoperative pulmonary complications are more likely to occur, and the attacks of asthma may be increased. Among the commonly used general anesthetic agents, we find that ether anesthesia abolishes vagal reflexes and relaxes the bronchial musculature because of its sympathomimetic action. By virtue of its stimulating effect on the respiratory mucosa, rate and depth of respiration are increased. Ether, however, causes increased secretion in light anesthesia, leading occasionally to increased postoperative pulmonary complications. This danger is lessened by deeper anesthesia, when secretions are abolished. The prolonged recovery period, with diminished pulmonary ventilation and absence of cough, predisposes to pulmonary complications. The advantages, however, outweigh the disadvantages, and in skilled hands ether is still the most useful agent.

Nitrous oxide and ethylene are not contraindicated at any time, as long as the patient is well oxygenated. Avertin causes relaxation of the bronchial musculature, but it also acts as a respiratory depressant. For this reason it is best employed in small doses and in combined anesthesia. Cyclopropone, in spite of the fact that it causes some irritation and a tendency to bronchial constriction, especially in higher concentrations, seems to work satisfactorily. The recovery period is short. Pentothal sodium, because of its parasympathomimetic action, also has a tendency to cause constriction of the bronchi, and yet seems to act favorably, par-

ticularly if used in combination with nitrous oxide. Some anesthesiologists see no contraindication in its use. I am of the opinion that it should not be used. Its prompt recovery period is much in its favor. Chloroform and ethyl chloride are bronchodilators, but are rarely used in present day anesthesia because of their toxic effects upon heart, liver, and kidneys. Vinethene has a greater tendency than ether to increase secretions and does not cause as great a relaxation of the bronchial musculature. It is more rapid in its action, however, but has a tendency to produce a certain amount of liver damage. For this reason it should not be used over long periods of time. Curare, although possessing no analgesic or anesthetic properties, is frequently used in conjunction with general anesthetic agents in order to produce greater muscular relaxation. Because of the liberation of histamine substances from the body tissues, the initial dose of this drug may produce bronchial constriction as an undesirable side effect. Repeated similar amounts of curare apparently do not cause further liberation of histamine substances. For this reason, such a bronchial spasm may be abolished by administration of further doses of the drug in question. Benadryl or Pyribenzamine given preoperatively may be beneficial.

Allergy, in association with drugs and agents used in connection with anesthesia, may be very troublesome to the anesthetist. Very few patients, if any, are ever tested for allergy or hypersensitivity to drugs or agents. The discovery of unfavorable reactions is usually made by history of some previous unsatisfactory result or by a reaction occurring for the first time.

Hypersensitivity to the commonly used inhalation agents is negligible. A few cases of ether allergy, however, have been reported. The anesthetist should be mindful of this condition if, for no apparent reason and shortly after the induction of anesthesia, the patient becomes cyanotic, with apparent circulatory collapse. Respiration, however, may continue to be undisturbed. Should ether be applied to the skin of such persons, there will be a complaint of burning and itching, followed by hyperemia and urticaria. The reaction may be severe enough to cause circulatory collapse.

Reports of allergic reaction resulting during cyclopropane anesthesia are not uncommon. Symptomatology will consist of edema of face, nose, lips, eyelids, conjunctiva, and larynx. Crowing and wheezing during respiration may occur, with probable pulmonary involvement. The crowing and wheezing may also be due to high concentrations of cyclopropane. Edema about the face can also result as an allergic reaction to the rubber mask, regardless of the inhalation agent used.

Pentothal, in addition to the unfavorable reactions which will be seen with the barbiturates (mentioned later), may cause coughing, hiccoughing, and sneezing. At present there exists no available evidence of allergic reaction resulting from the other most commonly employed general anesthetic agents.

A variety of drugs and agents may be used to perform local, regional or spinal analgesia. Sensitivity to spinal anesthetic agents is said to have occurred in rare instances. In all probability the technique, not the agent, was to be blamed. Pontocaine applied topically may produce immediate fatality. If used in the eyes, it may cause itching and edema of the lids, face, and parotid regions. Conjunctivitis, chemosis, and edema of the epithelium of the cornea are likely to occur. Pontocaine may cause urticaria, pain in the chest, and a feeling of choking, while nupercaine drops in the eye may initiate a reaction similar to pontocaine. Procaine may cause severe burning and itching at the site of injection, with accompanying dermatitis and vesicular areas. The neighboring lymphatics may be involved. Metycaine may also cause a dermatitis and itching. No matter what agent is used, one should always be mindful of a general reaction and be ready to administer immediate treatment for fall in blood pressure and convulsions.

Although the degree of toxicity varies among the agents, it is important to remember, however, that all will produce toxic symptoms that may become evident if sufficient dosage is used. Several methods are used in an attempt to inhibit toxic reactions. (1) The barbiturates may afford protection against local drugs. (2) Epinephrine, when applicable, is added to local anesthetic solutions to lessen their absorption. (3) The history may be suggestive. (4) Starvation and vitamin C deficiency lower the resistance to the toxic action of procaine. Dextrose and vitamin C prior to the use of large doses, therefore, may increase resistance to toxic effects, especially if a poor nutritional condition exists. (5) A skin test may be performed, raising one intradermal wheal with a small amount of the anesthetic agent to be used and another with physiologic salt solution as a control. The reaction may be local—burning, itching, redness, dermatitis, vesiculation, perhaps even involving the neighboring lymphatics —or systemic—dyspnea, agitation, disorientation, convulsions, et cetera. (6) Several drops of the agent may be instilled into the nostril and the blood pressure and pulse observed closely for twenty to thirty minutes. No marked changes should occur.

Two types of reactions may be recognized, neurological and circulatory. In the neurological type, the reaction is due to stimulation of the central nervous system. An early or stimulating phase may be evident, followed by a depressed phase. In the early phase, one can observe excitement, apprehension, headache, nausea, or vomiting, perhaps twitching of small muscles, leading to convulsions. Pulse and blood pressure vary; the skin is pale. As the reaction continues, blood pressure and pulse rate increase, as do also rate and depth of respiration. Evidence of cyanosis and dyspnea are discernible. In the depressed phase, there is paralysis of muscles, unconsciousness, absence of reflexes, circulatory failure, and no palpable pulse. Respiration fails, and the cyanosis becomes ashen-gray. Local anesthetic drugs, in small or thera-

peutic amounts, sometimes produce syncope and circulatory failure. This may be termed an idiosyncrasy. Pallor, tachycardia, circulatory collapse and skin reaction in the area of injection appear suddenly. It is important to remember that the barbiturates are ineffective in this type of reaction. I have spent some time dealing with the toxicity of local anesthetic agents merely to point out that many of the visible reactions are not a true hypersensitivity. They are due instead to toxicity resulting from injection of a large dose within a short period of time into a hypervascular area with sudden absorption, or the direct injection of the agent into the bloodstream.

Since ephinephrine is frequently used in anesthesia and allergy, it is well to remember that it, too, may produce toxic symptoms. This consists of pallor, fear, chilliness, tremor, tachycardia, headache, nausea, weakness, respiratory difficulty, dizziness, anxiety, and restlessness.

Unfavorable reactions resulting from the drugs most commonly used in preoperative medication should be mentioned. Opium and its derivatives may cause agitation, restlessness, dizziness, fainting, dyspnea and wheezing. Nausea and vomiting, together with violent and persistent retching, may follow the use of morphine. Abnormal respiratory depression may result. The patient may experience pain simulating acute gallbladder colic because of excessive contraction of the sphincter of Oddi. Tremors, delirium, convulsions and insomnia may occur in addition to urticaria, skin rashes, pruritus and sneezing. If a true idiosyncrasy exists, Pantopon, Dilaudid or Demerol may be used. There is a difference of opinion concerning these substitutes, particularly regarding Pantopon. I have used it in a few cases without any ill effects. Since Pantopon is close to 50 per cent morphine, by weight, it is sensible to assume that it would not be a good substitute.

The barbiturates often cause circulatory and respiratory depression and tend to increase the sensitivity of the laryngeal reflex. Allergic reactions present cutaneous lesions, erythematous dermatitis, and localized swelling, particularly of the eyelids, cheeks, or lips. The patient has a tendency to become excited and to appear inebriated. He may experience pain of a neuralgic, arthritic or myalgic type. Lassitude, vertigo, nausea, and vomiting are also possible in allergic reaction. Phenobarbital has been known to cause an exfoliative dermatitis which may be fatal. Rarely do patients present hypersensitivity to atropine; a rash may appear, especially on the face, neck and upper part of the trunk. There is circumoral pallor, tachycardia, mydriasis, and anhydrosis. Body temperature may be elevated with associated mental disorientation. There is dryness of mouth and difficulty in swallowing, restlessness, and headaches.

The unfavorable reactions of scopolamine are similar to those of atropine. The mental excitement may more readily progress to delirium. Local

edema of the uvula, epiglottis, glottis, et cetera, may occur and embarrass respiration.

In conclusion, we should remember that a great deal of the success of anesthesia in allergy depends upon the preparation of the patient, selection of premedication, and the choice of anesthetic agent and technique. Strict attention should be given to the postoperative care of the patient. We must not ignore the ability of the anesthetist. At times, it may be necessary to select a second choice of anesthetic agent or procedure, rather than a first choice, because of the capabilities of the anesthetist.

REFERENCES

1. Adriani, John: Techniques and Procedures of Anesthesia Springfield, Illinois: Charles C. Thomas, 1947.
2. Bonham, Russell F.: Cyclopropane anesthesia from an allergic standpoint Anesth & Analg, 18:288-291, (Oct.) 1939
3. Goodman, L., and Gilman A: The Pharmacological Basis of Therapeutics New York. The McMillan Company, 1941.
4. Gullen, Stuart C.: Anesthesia in General Practice Chicago: Year Book Publishers, Inc., 1946
5. Lundy, John S: Clinical Anesthesia Philadelphia W B Saunders Company, 1942
6. Perera, Charles: Ocular sensitivity to nupercaine Arch Ophth, 24:344-346, (Aug) 1940
7. Richards, Richard. Effects of vitamin C deficiency and starvation upon the toxicity of procaine Anesth J. Analg, (Jan & Feb) 1947.
8. Robinson, Saul, M D: An unusual cutaneous reaction to procaine hydrochloride Arch Dermat & Syph, 32 922, (Dec) 1935.
9. Stein, Herman B: Ether allergy: a case report Anesthiology, 6:515-521, (Sept) 1945

MICROPOWDERED AMINOPHYLLINE OR THEOPHYLLINE INHALATION THERAPY IN CHRONIC BRONCHIAL ASTHMA

(Continued from Page 523)

10. Prigal, S J; Brooks, A. M, and Harris, R: The treatment of asthma by inhalation of aerosol aminophylline J Allergy, 18 16, 1947
11. Segal, M. S, and Ryder, C M Penicillin inhalation therapy New England J Med, 236:132, 1947
12. Taplin, G V, and Bryan, F. A: The use of micronized therapeutic agents by inhalation with special reference to allergic pulmonary conditions Ann Allergy, 6 42, (Jan-Feb) 1948.
13. Taplin, G V, and Bryan, F A The administration of micronized therapeutic agents by inhalation or topical application Science, 105 502, 1947
14. Taplin, G V.; Cohen, S, and Mahoney, E. Prevention of postoperative pulmonary infection by inhalation of micropowdered penicillin and streptomycin J A.M A, 138:4, 1948
15. Truitt, E B, Jr; Carr, C J, Bubert, H M, and Krantz, J C, Jr.: The quantitative estimation of theophylline in blood J Pharm & Exper. Therap, 91:185, 1947.
16. Unger, L, and Gordon, F.: Bronchial asthma Critical review of the literature Ann Allergy, 6 165, 1948
17. Winter, I C Personal communication, July, 1948
18. Wyrens, R J Aminophylline in the treatment of bronchial asthma Nebraska M J, 32 273, 1947

THE TREATMENT OF INTRINSIC BRONCHIAL ASTHMA WITH AUTOGENOUS VACCINE

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BRONCHIAL asthma has long been conveniently divided into intrinsic and extrinsic types, depending upon whether the cause is endogenous or exogenous. It has been estimated by Rackemann[11] that 75 per cent of the cases of bronchial asthma are of the extrinsic type and 25 per cent are of the intrinsic variety. Actually, a combination of the two is more often encountered than either type in pure form. In all cases of bronchial asthma an "asthmatic diathesis" must be presupposed. Regardless of type, the pathologic physiology is identical.

Waldbott[20] questions the occurrence of "intrinsic asthma" as an entity on the grounds that there are always extrinsic causative factors, even though they are not discernible. However, many investigators, including Alexander,[2] Cohen,[5] Rackemann,[12] Tuft,[18] and Vaughn,[19] consider the classification as bonâ fide and useful in describing a common asthma syndrome which is most difficult to treat.

Cooke[6] presents an immunological classification of allergy in general, wherein he states that all antigen-antibody reactions are either immediate (within one hour) or delayed (several days). The immediate, or wheal type, reactions occur in the induced physiological phenomena, as anaphylaxis, and in the spontaneous syndromes having an hereditary background, such as extrinsic asthma, allergic coryza, urticaria and angioedema. The delayed, or inflammatory, type, reactions occur in the tuberculin type of reaction, the dermatitic type and the vascular type. Under the vascular type are included infective asthma, sinusitis, pericarditis and disseminated lupus. Thus, infective asthma is included in the same group as sinusitis, whereas extrinsic asthma is listed under those diseases that are due to causes which give the immediate type of allergic reaction. Whether there are different antibody mechanisms operating in the immediate and delayed reactions remains to be elucidated.

Rackemann[13] makes a distinction according to age. When the onset of bronchial asthma occurs before the age of thirty, he believes the condition should be considered allergic or extrinsic and treated as such, unless proven otherwise. When the onset occurs after forty, he believes the condition is likely to be due to causes other than typical allergic ones.

On the other hand, Rowe and Rowe[15] have found their cases of asthma in older individuals to be due to food and inhalant allergy with about equal frequency, as in all their asthmatic patients. They consider drug or bacterial allergy of rare etiological significance.

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Recognized intrinsic agents include: (a) physical allergy, which is usually manifested by a hypersensitivity to temperature change, (b) endocrine effects, such as the aggravation of asthma in women during their premenstrual cycle, (c) the psychogenic panel, which *per se* is purely intrinsic, (d) the "depletion" concept, a nonspecific state comprising malnutrition, weight loss and the so-called "lack of resistance" due to any cause whatsoever, but which, when corrected, tends to produce a beneficial effect on asthma, and (e) the bacterial infection component, with its implication of bacterial allergy, which is of prime importance.

Chronic infection in the paranasal sinuses is known to coexist with bronchial asthma in a high percentage of cases. Tuft[18] quotes Hansel regarding the incidence of sinus disease in several series of asthma cases as reported by various authors. The incidence varied from 26 per cent to 82 per cent. Infected tonsils and teeth are other foci to consider, but they are relatively rare in a specific sense, although dramatic relief of asthma is occasionally seen by their removal.

BACTERIAL ALLERGY

Alexander[2] has stated that bacterial allergy promises to surpass in scope and importance all other forms of allergy.

To appreciate the concept of bacterial allergy, one must believe in the old doctrine of focal infection. Indeed, they are one and the same. Originally, it was thought that a true bacteremia emanated from a focus of infection to cause disease in distant parts of the body. A later theory held that it was more likely that a bacterial toxemia took place, since only rarely could an actual bacteremia be demonstrated. Another theory, that of selective localization, was advanced to explain why only certain body structures were involved. The more modern view attributes the *modus operandi* to bacterial allergy.

In focal infection, bacteria are constantly present. However, skin tests for most bacteria are unreliable due to the inherent irritant qualities of these organisms, and although the delayed type of true local tissue allergy reaction is often seen, experience has shown no correlation of this reaction with the clinical picture, and specificity is not assured. Therefore, in this study, this procedure was omitted.

Zinsser and Parker[21] in 1923 suggested that in the course of any infection where bacterial foci are formed, there follows "a type of hypersusceptibility which is distinct from protein anaphylaxis" which might explain the remote injuries in infections, the causative bacteria of which were not true exotoxin producers.

Cooke[7] thinks that the absorption of bacterial substance or the products of their growth from areas of acute infection or chronic foci may produce different types of allergic disease. Organisms usually involved are various strains of streptococci, staphylococci and pneumococci. Infection as a cause of allergic disorders is not accepted as widely as it should

be because of the difficulty of proving the diagnosis, plus the fact that the precise mechanism is not yet known.

Nevertheless, bacterial allergy, as distinguished from simple bacterial infection, is serving increasingly to explain the etiology of many diseases, the pathogeneses of which have been unknown.[8] At the present time, that group of conditions included in the term "collagen disease" has an allergic etiologic concept. These diseases, characterized by fibrinoid degeneration in the connective tissues, include rheumatic fever,[4] rheumatoid arthritis, periarteritis nodosa,[14] disseminated lupus erythematosus[9] and others. Hypersensitivity to streptococci is believed to be essential to their pathogeneses. The same explanation has been offered in the case of glomerular nephritis.[10]

In discussing the role of bacterial hypersensitivity in rheumatic fever, Aikawa[1] mentions Coburn's prophylactic use of salicylates in rheumatic fever cases, which is generally considered to be quite effective. It is thought that salicylates have the power to block the antigen-antibody reaction by suppressing excessive antibody formation.[16] Aikawa also quotes the work of Wasson and Brown who administered repeated injections of a tannic acid precipitated toxin of a hemolytic streptococcus, with very good results (as far as recurrence was concerned) in a series of eighty rheumatic fever patients.

The role of the antibiotics in the therapy of intrinsic asthma is not as valuable as was first anticipated. Results indicate that they may be worthy of trial, since occasionally they have been effective in aborting an exacerbation. However, since allergic patients are prone to develop a sensitivity to penicillin and streptomycin, these products should be used with caution. Nevertheless, Baumann[13] and her co-workers treated a series of bacterial and mixed asthma cases with oral penicillin with the idea of mitigating the allergenic effects of any susceptible organisms present in the respiratory tract. The predominating organisms present before treatment were staphylococci and pneumococci. After treatment the pneumococci had largely disappeared, but the staphylococci remained, although they had been rendered "coagulase negative." Their results showed apparent control of the asthma in many cases for periods of six to sixteen weeks.

Desensitization in a nonspecific manner by the use of histamine has been disappointing in intrinsic and all other asthmas. Likewise, antihistaminic drug therapy has failed to achieve any notable success. However, very large doses are being tried in some of our cases on the theory that has been advanced of the possible significance of a quantitative histamine release.

Vaughn[17] has been using autogenous vaccines in bronchial asthma, starting with small doses and increasing the dose according to the reaction in each individual patient. He believes that both specific and nonspecific effects may be produced.

Cooke[7] adheres to the belief that a specific effect is obtained. He uses

vaccines prepared from cultures of sputum, sinus washings, and tissues removed at operation.

The viewpoint taken by many allergists concerning vaccine therapy in intrinsic asthma is that the method has a definite but limited application and that stock vaccines are about as effective as autogenous ones. However, it seems reasonable to assume that bacteria that are recovered from the patient's body are of more intrinsic value in obtaining a specific effect. The specific bacterial strains, the combinations of mixed organisms, the possibility of coexisting viruses, and other factors that are unknown, may be peculiar to the individual patient.

CLINICAL STUDY OF FIFTY CASES

Selection of Cases.—In this study, fifty cases of perennial bronchial asthma were observed and treated with autogenous vaccines during the past two years. They were selected cases insofar as they were diagnosed as being either of the pure intrinsic variety or of the mixed type with a definite intrinsic component. Reaction to extrinsic elements in the mixed cases was eliminated by appropriate desensitization to house dust, pollens and/or by the strict avoidance of foods or environmental factors discovered in the individual cases. When these procedures failed to ameliorate the symptomatology, these patients were also placed on vaccine therapy.

The clinical picture of typical intrinsic asthma has been described as beginning in an older individual with a dry cough, paroxysmal in nature, which progresses insidiously. Wheezing gradually supervenes, which, when established, makes for some degree of respiratory distress almost continuously. This picture is punctuated by attacks of greater severity, ranging to status asthmaticus. Blood eosinophilia is the rule. Skin tests are uniformly negative. Irreversible organic changes, such as emphysema and bronchiectasis, are prone to develop, and cor pulmonale is not infrequently seen in the later stages. Our impression of intrinsic asthma is similar, except that several cases occurring in children and younger adults have been included in our series. No good reason was apparent for excluding them from the intrinsic asthma classification merely because of their age.

Only those with clinically active chronic sinusitis were chosen for this study. Exacerbation of asthma was frequently found following upper respiratory infections (or flare-up of sinusitis); this sequence was always sought in the history. The coexistence of chronic sinusitis and bronchiectasis is well known, and the bronchosinusitis syndrome is frequently seen. These two associations are examples of symbiotic bacterial infection, wherein the infected sinuses are the original source of trouble. The analogy is extended to sinusitis and intrinsic bronchial asthma, but with a bacterial allergy mechanism rather than that of simple bacterial infection. In chronic sinusitis we have a steady, smoldering focus of infection, possessing continuous sensitizing potentialities. Both the conservative and radical treatments of sinusitis are notoriously ineffective for cure. It can

TABLE I. RESULTS OF AUTOGENOUS VACCINE TREATMENT OF INTRINSIC BRONCHIAL ASTHMA

Case	Age	Sex	Duration of Asthma	Positive Skin Tests to:	Type of Asthma	Chest X-ray before Vaccine Therapy*	Observation Period†	Organisms in Autogenous Vaccine	Results of Vaccine Therapy‡
1. N.H.	68	M	13 yrs.	Chocolate, orange, tobacco	Mixed	Emphysema + +	2 yrs.	Strep., and Staph. aureus	0
2. L.F.	35	F	10 yrs.	Several weed pollens	Mixed	Negative	2 yrs.	Staph. aureus and Gm. negative bacillus	Good
3. L.C.	11	M	8 yrs.	Several weed pollens. A few foods. Hog hair. Kapok.	Mixed	Moderate increase of hilar shadows	2 yrs.	Staph. aureus	0
4. P.R.	70	M	5 yrs.	Several foods. Several weed pollens.	Mixed	Emphysema + + Sl. honeycomb appearance of bases.	2 yrs.	Staph. albus	0
5. J.M.	31	M	5 yrs.	Several weed pollens.	Mixed	Negative	2 yrs.	Staph. aureus M. catarrhalis	Ex.
6. M.P.	12	F	6 yrs.	Cat hair. A few foods.	Mixed	Negative	2 yrs.	Staph. aureus Strep. and Gm. positive bacillus	Good
7. W.F.	40	M	4 yrs.	All negative	Intrinsic	Sl. increase B-V markings	2 yrs.	Staph. aureus and Gm. negative pleomorphic organisms	Ex.
8. F.W.	38	F	8 yrs.	All negative	Intrinsic	Negative	2 yrs.	Staph. aureus	0
9. O.K.	34	F	5 yrs.	Milk. Tomatoes.	Mixed	Increase B-V markings. Old fibrosis, Left apex.	2 yrs.	Staph. aureus	0
10. H.R.	64	M	10 yrs.	A few foods. Cattle hair.	Mixed	Calcified glands, left hilus. Otherwise negative.	2 yrs.	Staph. albus	Good
11. A.M.	61	M	20 yrs.	All negative	Intrinsic	Negative	1 yr.	Staph. aureus	Good
12. G.B.	37	F	14 yrs.	Spinach, mustard, tuna	Mixed	Diffuse fibrosis + +	1 yr.	Staph. aureus and M. catarrhalis	0
13. L.S.	15	F	3½ yrs.	All negative	Intrinsic	Negative	1 yr.	Staph. albus	Ex.
14. R.B.	34	F	2 yrs.	A few weed pollens	Mixed	Emphysema + + Honeycombing both bases +	1 yr.	Gm. positive cocci and bacilli	0
15. G.R.	24	M	4 yrs.	All negative	Intrinsic	Sl. increase B-V markings	1 yr.	Staph. aureus and Diphtheroids	Ex.
16. P.H.	30	M	9 yrs.	All negative	Intrinsic	Negative	1 yr.	Staph. aureus and Diphtheroids	Ex.
17. P.D.	53	F	6 yrs.	A few foods	Mixed	Sl. increase B-V markings	1 yr.	Staph. aureus	Ex.
18. D.R.	16	F	1 yr.	A few foods. Common weed pollens	Mixed	Negative	1 yr.	(a) Staph. aureus (b) Staph. aureus	0
19. A.S.	38	M	10 yrs.	House dust, tobacco, and several foods	Mixed	Emphysema + + Increased B-V markings	1 yr.	Staph. aureus and Strep.	0
20. L.G.	32	M	3 yrs.	House dust. Moulds alb., corn, wheat	Mixed	Infiltration, left apex	11 mos.	Staph. aureus and Diphtheroids	Good
21. T.C.	23	M	6 yrs.	All negative	Intrinsic	Increased B-V markings	11 mos.	Staph. aureus	Good
22. A.S.	7	M	3 yrs.	House dust, horse and dog hair	Mixed	Negative	10 mos.	Staph. aureus	Ex.
23. B.K.	36	M	4 yrs.	All negative	Intrinsic	Negative	10 mos.	Staph. aureus	Good
24. A.B.	37	M	10 yrs.	All negative	Intrinsic	Increased B-V markings; infiltration both apices	9 mos.	Staph. aureus	Ex.
25. E.K.	30	M	2 yrs.	All negative	Intrinsic	Increased B-V markings	9 mos.	Staph. aureus and Gm. positive bacillus	Ex.

TABLE I RESULTS OF AUTOGENOUS VACCINE TREATMENT OF INTRINSIC BRONCHIAL ASTHMA—CONTINUED

Case	Age	Sex	Duration of Asthma	Positive Skin Tests to:	Type of Asthma	Chest X-ray before Vaccine Therapy*	Observation Period‡	Organisms in Autogenous Vaccine	Results of Vaccine Therapy†
26. E.N.	14	M	2 yrs.	A few foods	Mixed	Negative	8 mos.	Staph. aureus	Ex.
27. R.P.	57	M	15 yrs.	A few foods	Mixed	Negative	8 mos.	Staph. aureus and Strep.	Ex.
28. R.L.	47	M	16 yrs.	All negative	Intrinsic	Emphysema ++	8 mos.	Staph. aureus	Good
29. O.H.	77	M	2 yrs.	All negative	Intrinsic	Negative	7 mos.	Staph. aureus and strep.	Good
30. E.K.	33	F	15 yrs.	Goose feathers, tobacco, oats, tomatoes, lettuce	Mixed	Increased B-V markings. Stabilized infiltration L. 2nd I.S.	7 mos.	Staph. aureus	0
31. F.V.	12	M	2½ yrs.	Goose feathers and a few foods	Mixed	Several small areas calcification both upper lobes	6 mos.	Staph. aureus	Ex.
32. R.S.	33	F	23 yrs.	All negative	Intrinsic	Increased B-V markings. Few calcified areas upper lobes	6 mos.	Staph. aureus and Pneumococcus	Ex.
33. E.S.	61	M	10 yrs.	Several foods	Mixed	Negative	6 mos.	Staph. aureus	Good
34. N.F.	49	F	12 yrs.	All negative	Intrinsic	Increased B-V markings	6 mos.	Staph. aureus	0
35. J.G.	45	F	9 yrs.	Goose feathers, wheat	Mixed	Negative	6 mos.	(a) Staph. aureus (b) Staph. aureus and M. catarrhalis	Ex.
36. G.E.	72	M	7 yrs.	All negative	Intrinsic	Emphysema ++	6 mos.	Staph. aureus and M. catarrhalis	0
37. R.H.	54	F	20 yrs.	Several foods. Several weed pollens.	Mixed	Negative	6 mos.	Staph. aureus	Good
38. W.H.	48	M	5 yrs.	Monilia albicans, Chaetomium glob.	Mixed	Increased hilar shadows	5 mos.	Candida (Monilia) albicans	Ex.
39. R.V.	29	M	5 yrs.	All negative	Intrinsic	Negative	5 mos.	Staph. aureus	Good
40. A.C.	32	F	1 yr.	Goose and chicken feathers, chalk, American cheese	Mixed	Increased B-V markings	5 mos.	Staph. aureus and M. catarrhalis	Good
41. W.B.	56	F	2½ yrs.	Tobacco and a few foods	Mixed	Increased B-V markings. Old infiltration, left apex.	5 mos.	Staph. aureus and Gm. positive bacilli	Good
42. N.P.	46	M	15 yrs.	All negative	Intrinsic	Increased B-V markings	4 mos.	Staph. aureus	0
43. A.W.	65	M	10 yrs.	All negative	Intrinsic	4 mos.	4 mos.	Staph. aureus and Strep.	Good
44. N.J.	45	F	2 yrs.	A few foods	Mixed	Negative	4 mos.	Staph. aureus	Ex.
45. O.H.	31	F	10 yrs.	All negative	Intrinsic	Negative	4 mos.	Staph. aureus	Good
46. A.A.	26	M	8 yrs.	All negative	Intrinsic	Negative	3 mos.	Staph. aureus	Good
47. S.C.	8	F	5 yrs.	Common weed pollens	Mixed	Negative	3 mos.	Staph. aureus	Ex.
48. A.T.	8	F	4 yrs.	Common weed pollens. Hormodendron, Alternaria	Mixed	Negative	3 mos.	Staph. aureus	Ex.
49. S.P.	53	F	5 yrs.	Common weed pollens	Mixed	Increased B-V markings. Pleural thickening	3 mos.	Staph. aureus	Good
50. E.L.	54	M	10 yrs.	All negative	Intrinsic	Negative	3 mos.	Staph. aureus	Good

*In this column, B-V=bronchovascular.
†Length of time patient was observed from the time vaccine therapy was begun.
‡In this column, Ex. (Excellent)=patient relieved; Good=definite amelioration, but not alleviation; 0=no effect.

be stated unequivocally that there was a corresponding improvement observed in most instances regarding the sinusitis increment in those cases whose asthma responded to vaccine treatment.

Methods and Procedure.—Co-operation with the ear, nose and throat and clinical laboratory departments was secured. With each patient swabs were taken from the semilunar fossa of the middle meatus (just below the middle turbinate) where all the paranasal sinuses drain, with the exception of the posterior ethmoids and the sphenoids. Then, according to the method of Todd and Sanford,[17] the swabs were cultured, after which bacterial suspensions were made up in normal saline solution. After sterilization and counting, the suspensions were diluted to the strength of 1,000 million organisms per cubic centimeter, put up in quantities of 20 cubic centimeters in sterile rubber-topped vials and stored in the refrigerator. The organisms that were obtained from each patient and used in his vaccine are given in Table I.

Prior to vaccine therapy, each patient was given 100 scratch tests for the common foods and the pollens and fungi peculiar to this region. Environmental factors also tested for were: house dust, kapok, tobacco, tobacco smoke, newspaper, goose feathers, chicken feathers, horse dander, cattle hair, cat hair, dog hair, hog hair, sheep wool, orris root, cotton and chalk. The chest of each patient was also x-rayed.

The process of desensitization (hyposensitization) was carried out on individual patients as follows: Commencing with a dose of one minim (62.5 million organisms), injected subcutaneously, the dose was increased routinely by one minim for each injection, given at five-day intervals. When the dosage of sixteen minims was reached (1,000 million organisms), subsequent injections were kept at this dosage and were made once weekly. Adjustment of dosage because of reactions was carried out as necessary. Drug therapy was kept at a minimum in order to evaluate the results properly, and it was only used when absolutely necessary during the early part of the desensitization program. The period during which each patient was observed from the time vaccine therapy was instituted varied from two months to two years.

The total elapsed time required to complete the desensitization program for the average patient was five months, at which time his vaccine supply was exhausted and the treatment was terminated. Local reactions, consisting of redness, pain and edema, were frequent and were seen in nearly all patients at some time. Systemic reactions (exacerbation of asthma) were seen rather frequently. Most reactions were of the delayed type, and they indicated that the vaccine was potent. In the average favorable case, subjective and objective improvement was very evident somewhere between the fifth and eighth dose, or within the first four to six weeks. The data for each case are given in Table I.

Results.—As may be seen from Table I, of the fifty patients, eighteen (36 per cent) obtained excellent results, nineteen (38 per cent) good results, and thirteen (26 per cent) no favorable effects from the vaccine therapy.

Twenty-one cases had purely intrinsic asthma, and twenty-nine had mixed asthma. However, the extrinsic factors of the latter were considered to be under control. Favorable (excellent or good) results were found in seventeen (81 per cent) of the intrinsic, and in twenty (69 per cent) of the mixed asthma cases.

Of the fifty autogenous vaccines, thirty-one were prepared from single strains of bacteria and nineteen from two or more strains. Staphylococcus aureus was by far the predominating bacterium that was isolated. It was present in pure culture in twenty-seven cases and in mixed culture in nineteen others. Staphylococcus albus was isolated in pure culture from three patients and Candida albicans from one. Favorable results were obtained in twenty-three cases (74.2 per cent) with the thirty-one single strain vaccines, and in fourteen cases (73.7 per cent) with the nineteen mixed strain vaccines.

All the patients who had obtained favorable results either had had no roentgenological abnormalities or only minor ones, except one (Case 28) whose chest film had revealed moderate emphysema. On the other hand, of those that were not affected favorably, eight or (61 per cent) had shown roentgenological evidence of definite pathologic conditions.

The patients who were benefited by vaccine treatment had had asthma for an average duration of 7.3 years; those who were unimproved had had the disease for an average duration of 8.8 years.

There were twenty-one females and twenty-nine males. In the former group 66.6 per cent received favorable results as compared to 79.3 per cent of the latter.

The ages of the patients ranged from seven to seventy-seven years. The average age of those who obtained favorable results was forty years, and of those with unfavorable results, forty-eight years. The best results were seen in patients in the first, second, third and fourth decades.

There was no correlation of therapeutic results with the length of time the patients were observed.

In three cases (Cases 18, 22 and 35) new vaccines were prepared and the desensitization scheme was reinstituted. These patients are still receiving vaccine. In Case 18 an attempt to realize a better outcome is being made, since the first trial was unsuccessful. In Case 22 excellent results were obtained with vaccine therapy after hyposensitization to house dust had failed to relieve the symptoms. The patient was symptom free for ten months following vaccine treatment. Just recently, mild daily wheezing and postnasal discharge have recurred. A new vaccine has been prepared, and he is undergoing a second period of desensitization. Resumption of treatment was carried out in Case 35 at the patient's request. She

stated at the end of her period of treatment that she hadn't felt so well in years, and she was apprehensive about suspending therapy. Consequently, a new vaccine was made and treatment resumed.

Case 34 was the only one in the series in which it was necessary to discontinue injections because of unfavorable reactions. This patient developed such severe local and general symptoms, even after the injection of repeated serial dilutions, that it was decided it would be wiser to discontinue vaccine therapy entirely.

Case 38 is unique in this series by reason of having a fungus etiology. Repeated sinus and sputum cultures yielded only Candida albicans. Increasing doses of potassium iodide, given over a period of two months, failed to ameliorate the chronic productive cough and wheezing. The patient has been in the process of desensitization to this fungus now for five months and has been symptom free for approximately four months.

A discussion of bronchial asthma would be incomplete without mentioning the psychogenic element which is so often encountered. Where it is predominant, all therapy is ineffective until this factor is controlled. It is a well-known clinical observation that a psychic shock can precipitate or aggravate an attack. In fact, an old theory which brands bronchial asthma as a pure neurosis is being revived. However, one should assume a tolerant view and realize that, in addition to a possible causative role, the asthma itself understandably renders the patient more emotional. Thus, a vicious circle reaction is introduced.

In Case 9 the patient had frequent episodes of status asthmaticus which eventually responded to different combinations of therapy. This case is complicated by a severe involutional melancholia. No benefit has been derived from vaccine.

The patient in Case 12 was doing well on her desensitization program until she was in a car accident in which she sustained a fractured tibia and facial lacerations. There followed a long period of litigation with the patient as the plaintiff. During this time she exhibited frequent attacks of dyspnea, often during which no râles could be heard. The lawsuit has recently been settled quite favorably for the patient, and her bronchial asthma has taken a proportionately satisfactory turn for the better.

In Case 45 the patient was showing definite improvement on vaccine therapy when she developed a manic-depressive psychosis, manic phase, with exacerbation of her asthma, which rapidly merged into a status asthmaticus. She was transferred to a mental hospital where shock therapy was instituted, resulting in remissions for both the psychosis and the asthma in a relatively short time. She has resumed desensitization therapy, and no further asthma has been noted.

SUMMARY AND CONCLUSIONS

1. Fifty cases of intrinsic and mixed bronchial asthma with associated chronic sinusitis were treated with autogenous vaccines and observed for

varying periods of time. Favorable results were realized in thirty-seven cases (74 per cent), indicating that this form of management is worthwhile when dealing with an asthmatic syndrome in which ordinary treatment has little to offer. The best results were obtained in patients who were in the first four decades of life and in those whose chest x-rays had revealed only minimal evidence of organic changes or none at all. This is in accord with the therapy of disease in general; that is, better response is usually obtained in younger individuals and before structural pathological changes have occurred.

2. Chronic sinusitis is believed to be the most important focus of infection in intrinsic asthma. Staphylococcus aureus was the predominant bacterium encountered.

REFERENCES

1. Aikawa, J. K.: Hypersensitivity and rheumatic fever. Ann. Int. Med., 23: 969-998, 1945.
2. Alexander, H. L.: Synopsis of Allergy. Pp. 88 and 200. St. Louis: C. V. Mosby Co., St. Louis, 1941.
3. Baumann, F.; Crump, J.; Arthurs, A. C.; Seagar, L. D., and Miller, R. E.: Use of oral penicillin in treatment of bacterial asthma. J. Allergy, 17:265-270, 1946.
4. Coburn, A. F.: Observations on the mechanism of rheumatic fever. Lancet, 2:1025, 1936.
5. Cohen, M. B.: Bronchial asthma: classification based on etiological and pathological factors. Ann. Int. Med., 20:590-596, 1944.
6. Cooke, R. A.: The immunology of allergic disease. Am. J. Med., 3:523-533, 1947.
7. Cooke, R. A.: Allergy in Theory and Practice. Philadelphia: W. B. Saunders Co., 1947.
8. Editorial: Allergy in the production of lesions in disease. J.A.M.A., 133:776, 1947.
9. Fox, R. A.: Disseminated lupus erythematosus—an Allergic disease? Arch. Path., 36:311, 1943.
10. Kay, C. F.; Lucchesi, P. F., and Rutherford, R. B.: An experimental investigation of an immunologic mechanism as the cause of glomerulonephritis. J. Immunol., 42:369, 1941.
11. Rackemann, F. M., in Cecil, R. L.: Textbook of Medicine. P. 544. Philadelphia and London: W. B. Saunders Co., 1947
12. Rackemann, F. M.: The doctor and the patient with asthma. Chicago M. Soc. Bull., (May 15) 1948.
13. Rackemann, F. M.: A working classification of asthma. Am. J. Med., 3:601-606, 1947.
14. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins Hosp., 72:65, 1943.
15. Rowe, A. H., and Rowe, A. H., Jr.: Bronchial asthma in patients over the age of fifty-five years. Ann. Allergy, 5:509-518, 1947.
16. Swift, H. F.: The action of sodium salicylate upon the formation of immune bodies. J. Exper. Med., 36:735, 1922.
17. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods. Tenth edition, pp. 811-816: Philadelphia: W. B. Saunders Co., 1946.
18. Tuft, L.: Clinical Allergy. Pp. 257 and 275. Philadelphia: W. B. Saunders Co., 1937.
19. Vaughn, W. T.: Practice of Allergy. Pp. 695 and 700. St. Louis. C. V. Mosby Co., 1939.
20. Waldbott, G. L.: Is there an intrinsic asthma? Ann. Int. Med., 26:863-872, 1947.
21. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: Immunity Principles and Application in Medicine and Public Health. Fifth Edition, p. 431. New York: The Macmillan Co., 1941.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE von PIRQUET GOLD MEDAL

One of the outstanding features of the old annual Forums on Allergy was the presentation of the von Pirquet Gold Medal for outstanding contributions to clinical allergy. Consequently, it was first presented to Bela Schick at the Indianapolis meeting of the Forum. W. W. Duke, "Father of Clinical Allergy," received the second medal at the Detroit meeting. The following year Arthur Coca received the award at the Cleveland session and then Robert Cooke the following year at the St. Louis meeting. The last medal was bestowed upon Milton J. Rosenau and since that time no awards have been made.

Later the same year the College initiated graduate instructional courses in allergy under the auspices of medical schools, and this policy was followed shortly afterwards by the Academy. It was therefore considered unnecessary to continue the old "one man society," and the meetings of the Forum were discontinued as well as the medal awards.

I am happy to announce that during my presidency the Board of Regents of the American College of Allergists has accepted the gift of the dies for the von Pirquet medal and will re-establish awarding this medal for outstanding contributions to clinical allergy—scientific or organizational. The first award by the Board of Regents of the College will be made at the St. Louis meeting.

SIMULTANEOUS SESSIONS

It has always been my personal belief that there are certain advantages in having simultaneous sessions during a medical convention. The secret of the success of the old annual Forums on Allergy was due to this policy. Every phase of allergy was presented, but no member could hope to attend all of the sessions.

Since most of the papers presented at the College annual convention are published later, it is even more important to have a choice for the members. From an organizational point of view, such an arrangement of the program assures a greater attendance next year. It gives many men a chance to present their material who otherwise would not have the opportunity. It provides smaller and more intimate groups for the discussions following the papers. It gives the essayist a sense of pride in that he knows those present are there to hear him and not because there is nothing else to do around the convention.

This year two sets of papers will be read simultaneously. This arrangement will serve the greatest number most advantageously and will be best for the College and consequently for American Allergy.

JONATHAN FORMAN, *President*

Progress in Allergy

BRONCHIAL ASTHMA V

Critical Review of Literature

LEON UNGER, M.D., F.A.C.A., and BENJAMIN F. GORDON, M.D., F.A.C.A.
Chicago, Illinois

(Continued from May-June issue)

HISTAMINE IN THE TREATMENT OF ASTHMA

Histamine itself causes bronchospasm but it has been tried in increasing dosage (as a form of hyposensitization). Tuft[516] warns of the danger (shock, increased asthma, cardiac upsets), and says the procedure is ineffective in those allergies in which there is a specific antigen-antibody reaction as in hay fever or allergic asthma. It may be beneficial in conditions like urticaria or physical allergy in which circulating antibodies and positive skin reactions are absent. Any good results are inferior to those obtained by specific avoidance and hyposensitization. Good results by histamine-hyposensitization in four cases of bronchial asthma are reported by Giordano,[221] and in two cases of asthma and three of asthmatic bronchitis by Giovannoli,[222] with failure in one asthmatic and aggravation in another by Rockwell.[423] Rockwell gave injections of certain derivatives of histamine; he feels that if a substance could be made which when injected would slowly liberate histamine such therapy would be better than the present method of frequent intravenous or subcutaneous injections of histamine itself.

Scrafini and Biozzi[159] found no significant change in blood histamine in normal subjects after specific physical exercise; but in patients with hay fever and asthma an increase occurred within five to ten minutes. In one patient a sudden and remarkable increase occurred and with it an attack of asthma. Blood histamine level in normals is not changed from one to fifteen minutes after a subcutaneous injection of histamine; but the level is increased in allergic patients and with this, in some cases, symptoms increased.[457] Horstmann and Kjerulf-Jensen[264] injected 0.1 to 0.5 mg. histamine and brought on typical attacks of asthma or marked dyspnea in fifteen of twenty patients with latent bronchial asthma. This effect could be depressed or prevented by intravenous injections of aminophyllin.

Curry[140] discusses the clinical uses of histamine and histaminase. The latter seems clinically valueless. Intravenous injections of 0.01 to 0.04 mg. of histamine base in asthmatic patients causes an asthma-like attack with reduction in vital capacity. (This fact might aid in ruling out hysteria or malingering). Inhalation of mecholyl gave similar results.[141] Curry and Lowell[142] found that intravenous injections of up to 0.04 mg. histamine or intramuscular injections of up to 6 mg. mecholyl caused no real reduction in vital capacity in normal subjects. But in asthmatics both these drugs cause attacks of asthma with reduced vital capacity. The response to mecholyl is prevented or markedly inhibited by atropine but not by Benadryl or Pyribenzamine. But these latter two drugs protect against histamine, and atropine is relatively ineffective in this regard. When they induced asthma by inhalation of pollen extracts neither atropine nor antihistaminic drugs gave protection or relief, but aminophyllin and epinephrine protect against all three, i.e. histamine, mecholyl and pollen.

Curry and Lowell also believe that pure extrinsic asthma is rare; most patients are allergic to one or more allergens, but they have asthma at odd times, apparently unassociated with their allergens. Attacks are brought on by cold air, steam, extremes of temperature, laughter, cough, emotional upsets, respiratory infections, smoke, particulate matter, soap flakes, strong odors and irritating gases. The non-specific character and the variability of the stimuli which can cause wheezing is striking. Histamine or other stimulants of the parasympathetic nervous system may be an added insult. [We call such stimuli "contributory" factors.]

Rose[425] discusses histamine in anaphylaxis and allergy. Tissue histamine is chiefly found in the lungs and liver. Seventy to ninety per cent of blood histamine is held in an inactive state within the white blood corpuscles; the rest circulates in a free state in plasma or is held within erythrocytes. The blood histamine con-

tent is not significantly changed in patients either during or between attacks of asthma, but he found a marked increase of histamine in stools of asthmatic patients as compared with normal subjects. Trethewie[514] found practically no histamine in fetal lungs, but at birth the histamine content is very high, greater than in any other period up to forty weeks. Gaddum[211] discusses many phases of histamine.

ANTIHISTAMINIC DRUGS IN TREATMENT OF ASTHMA

The flood of papers regarding the value of these drugs continues, with new members. Everyone now is convinced that all of these drugs give more or less symptomatic relief in some allergic conditions, especially hay fever, allergic rhinitis, urticarias and atopic dermatitis. Their value in asthma is still disputed. We shall now endeavor to appraise each of these drugs as regards asthma and then compare members of the group with one another.

Hydryllin contains 25 mg. Benadryl and 100 mg. aminophyllin. The former is antihistaminic and a good sedative; the oral use of the latter is of some value in asthma, thought not as effective as when given intravenously or even rectally. The committee on Therapy of the American Academy of Allergy found that Hydryllin was more effective in all types of bronchial asthma than any other of the group. In 397 cases, the drug gave good results in 119 (30 per cent), fair results in eighty-two (21 per cent), and was ineffective in 196 (49 per cent). Side reactions in a total of 1,570 cases (all types of allergy) were "severe" in 1,219 (72 per cent), moderate in 314 (20 per cent), and absent in 126 cases (8 per cent). One should add that even the "severe" reactions were not alarming.

Markow and his associates[332] found Hydryllin beneficial in 70 per cent of forty-six cases of asthma. Reactions forced abandonment of the drug in 15 per cent of the cases. Levin and Moss[296] obtained 50 to 100 per cent relief for from three to six hours in twenty-two asthmatic patients, but benefit in only one of three cases in which bronchial infection was also present. Side reactions were less than with Benadryl or Pyribenzamine. Segal and co-workers[453] found that two tablets of Hydryllin did not give significant protection against histamine shock for one to one and one-half hours after ingestion, but they then gave complete protection for seven hours. There was less protection against mecholyl. [The addition of aminophyllin which is an excellent bronchodilator to Benadryl makes a fairly good anti-asthmatic combination.] Brown and Brown[89] found that Hydryllin tablets, three or four a day, gave good results in asthma: 100 per cent relief in fifteen of thirty-four cases, with partial relief in ten more cases. The relief lasted over thirty minutes in thirty-one attacks and over an hour in twenty-two.

Phenergan (3277RP) is the name given to one of an entirely new series of chemicals developed by the French school under the leadership of Vallery-Radot, Halpern, Hamburger, Cruchand, and Blamoutier.[231,232,235,526,527,528,529] All of these chemicals belong to the thiodiphenylamine group. Among those studied 3277RP has especially marked antihistaminic and anti-anaphylactic properties. It can protect a guinea pig against 1,500 lethal doses of histamine, and 0.1 mg. per kg. protects a guinea pig against fatal anaphylactic shock. It is roughly equivalent to Antergan in its action on the bowel and bronchi; its antihistaminic power is about forty times that of Antergan, and its antianaphylactic power five times greater. Therefore the antihistaminic shock action does not run parallel with the antihistaminic activity as regards particular functions. The new chemical must possess some other factor.

Halpern[231] points out that marked tissue eosinophilia in the lungs is present in guinea pigs which have experienced a severe but not fatal anaphylactic shock (insufficient antigen or antihistamine protection). "All around the bronchioles are masses of eosinophiles, invading the columnar epithelium of the bronchi, often bursting into the lumen of the bronchi and even present in the intrabronchial exudate." This pulmonary eosinophilia is absent or slight when preliminary antihistaminic drug prevents or aborts shock.

In the experimental animal, 3277RP is about fifteen times as effective as Pyribenzamine and it has a low toxicity. It has no significant effect on the promotion of gastric secretion by histamine. Excellent results were obtained in urticaria, even in cases in which other antihistaminic drugs had failed, and also in angioneurotic edema, acute eczema, pruritus, purpura, hay fever and migraine.

Its effect in asthma is uncertain. In one report[529] the majority of twenty-one cases with no definite allergic etiology remained unaffected. In a later report,[528] in twenty-one cases, ten were not improved, seven obtained fair results, with four

perfect results. In this paper it is implied that the antiallergic action of 3277RP does not seem to be due to its antihistaminic power—perhaps it actually prevents antigen-antibody reaction. The average daily dosage is 0.05 to 0.1 gm. The only unpleasant side effects in patients are occasional somnolence, vertigo and inability to concentrate; these reactions disappear in a few days even if the drug is continued; these side effects were usually controlled by Benzedrine. The French authors believe this drug gives better results in asthma than do Antergan, Neoantergan and American drugs of this type.

Previous injection of 3277RP[232] prevents, in 100 per cent of cases, acute pulmonary epinephrine-induced edema in rabbits. When given after the onset of edema the drug appears curative. A similar effect occurred in rabbit lung edema induced by chloropicrin (a war gas), and the drug also seemed curative. In eight of ten allergic patients there was an extremely great increase in capillary resistance beginning one to two hours after injection of the drug and persisting up to forty-eight hours. This effect was not noted in non-allergic persons. Some drugs of this series also show local anesthetic powers four to six times that of cocaine. This anesthetic factor may be responsible for some of the therapeutic properties of these drugs.

Pellerat and associates[376] discuss the effect of these drugs on blood histamine.

Trimeton (Schering) is another new antihistaminic. Brown, in a study of 227 allergic patients[85] obtained excellent results in 61 per cent and good in another 22 per cent; in only 6 per cent was it necessary to stop the drug because of side effects. In hay fever with mild extrinsic asthma good results were obtained in 80 per cent (twenty-one patients). Wittich[561] tried the drug in 125 cases. In thirty-eight cases of asthma (nine with hay fever) good results were obtained in six cases, fair in four and poor in twenty-eight. Wittich says a tablet of Trimeton before injections will enable larger dosages of antigens without reactions. [This procedure, like that of mixing epinephrine with extracts, is open to objection in that the reaction may only be delayed. Personally, we prefer no reactions but they do occur, even with care, and when they occur we would rather have the patient in our office than on the way home.]

Neohetramine (Nepera-Wyeth) was studied by Seudi, Reinhard and Dryer.[450] Experimentally, it is about half as toxic as other antihistaminic drugs yet gives excellent protection against anaphylactic shock in actively and passively sensitized guinea pigs. Waldbott and Borden[511] gave about 50 mg. every four hours to 279 allergic patients. Good results were obtained in thirteen (17 per cent) of seventy-five cases of asthma—just about what other antihistaminic drugs have done. Criep and Aaron[137] tried the drug in 249 allergic patients. In thirty-three asthmatics complete relief was secured in 12 per cent, and moderate in 27 per cent. The authors are not impressed as regards asthma—"clinically Neohetramine was found to be of as much value as the other antihistaminic drugs in the treatment of allergic states." Roberts[419] reviews the literature, with a study of 874 allergic cases. "All investigators concurred that Neohetramine is the least toxic of all antihistaminics now in general use." In 189 collected cases of asthma, benefit was obtained in eighty-two (43 per cent), especially in those with an associated spasmodic cough.

Decapryn (Merrell) was first used clinically by McQuiddy.[323] He gave only 12.5 mg. twice daily to 103 allergic patients. Approximately 50 per cent of the asthmatic patients experienced some relief. Feinberg and Bernstein[181] studied the drug pharmacologically; it is highly effective in the inhibition of cutaneous histamine reactions. There were good results in 118 cases of hay fever and allergic rhinitis. Although, as with other antihistaminic drugs, no appreciable relief of asthma was observed, the asthma patients in whom hay fever was associated were effectively relieved of their hay fever. Sheldon and his associates,[466] in a study of 117 patients, found that Decapryn relieved satisfactorily the wheezing of fourteen of twenty-six asthmatics (54 per cent); chest tightness was relieved in 50 per cent, sputum in 66 per cent, and cough in 80 per cent. Brown and his co-workers[88] studied the drug in 140 consecutive patients. In forty-one cases of asthma excellent results were obtained in eight, moderate in nineteen and negligible in fourteen. In twelve patients with bronchial asthma and allergic coryza excellent relief of nasal symptoms occurred in eight, moderate in two; in three of these, bronchial symptoms were almost entirely overcome.

Histadyl (Lilly) and *Thenylene* (Abbott) are new drugs, identical in structure. Pierce and Mothersill,[385] in seventy-seven allergic patients obtained complete relief in

twenty-one ragweed-hay fever sufferers (daily dose 100 mg.). Poor results followed its trial in six asthmatic patients. Commenting on this article, Wittich[117] says "There is accumulating evidence that all of these so-called 'antihistaminic drugs' have a strong hypnotic action and the clinical results obtained are a result of this profound sedation rather than any neutralizing action of histamine. The histamine theory as a primary, rather than an incidental, factor in hypersensitive states is becoming increasingly illogical, with the increasing observations of sound biochemists and immunologists. However, when the release of histamine is the causative agent the use under certain conditions of these antihistaminics in some allergic diseases is justified and may give relief in cases where little or no relief was achieved before. . . . If continued too long, some patients develop a type of asthma which is difficult to manage. In hay fever patients, continued use may block the 'shock' organ in the upper respiratory tract and shift it to the lower respiratory tract. . . . A group of patients may have excellent results when being relieved of nasal symptoms but develop asthma at the end of the season. A well regulated course of inoculations with a good pollen extract remains still the safest and best treatment of pollen allergy. Frequently, the best 'antihistamine' drugs in connection with immunization measures are epinephrine and ephedrine, or similar vasoconstrictors, in conjunction with the use of the barbiturates."

Feinberg and Bernstein[170] found that the drug did not appreciably alter the dyspnea in thirty asthmatic patients, although the preasthmatic, spasmodic cough was decidedly helped in six of nine patients. The drug seems not quite as effective as Pyribenzamine, though it may be better in selected cases. Friedlaender and Friedlaender[196] likewise found no striking benefit in twenty-one asthmatic patients (improvement in seven). Like the others, Martins,[571] in eight cases of hay fever-asthma, found that Thenylene failed to help the asthmatic symptoms, but it did relieve the hay fever in seven of these patients.

Antistine (Ciba) has been investigated by several. Friedlaender and Friedlaender[195] tried it in 100 patients with palliative relief in 59 per cent of cases of allergic rhinitis and 37 per cent of asthmatics. About 50 mg. Pyribenzamine seemed about as effective as 100 mg. Antistine; the latter gives less side reactions. Skoubl[475] obtained no benefit in twelve cases of bronchial asthma, and Hughes in thirteen asthmatics, five with hay fever, had good results in five and fair in four more.[571,572] Walton, in eighty-three cases,[519] obtained improvement in only one of fourteen cases of asthma.

Neo-Antergan (Merck) was given in 100 to 400 mg. dosage three times daily to eighteen asthmatics, with good results in five, fair in two, and poor in eleven; in eight cases of pollen asthma: good results in two (Report Committee Therapy American Academy Allergy).[411] Southwell (In England the name Anthisan is used for Neo-Antergan) found no benefit from the drug in twenty-five specially selected and carefully observed cases of asthma. The hay fever symptoms in fifteen hay fever-asthma cases were markedly benefited. Southwell warns of success from a psychic standpoint (new drug); in fact those asthmatics who were given dummy pills reported slightly more improvement than those who took the Anthisan.[453] Hunter and Dunlop[573] also used dummy pills alternating with the drug and conclude that Neo-Antergan is of no value in preventing attacks of bronchial asthma. Herxheimer[255] condemns these methods of evaluation. Statements of patients cannot be relied on; one must use spirometric (vital capacity) readings to determine the value of a drug. Herxheimer[254] takes three readings in each patient. In many years of experience he has never seen an asthmatic patient able to increase his vital capacity by even 300 c.c. from one hour to another by will power or suggestion from the outside. But this has happened repeatedly under the influence of epinephrine, Alendrin (Isuprel), aminophylline, Neo-Antergan (Anthisan), and other drugs. There is therefore no need for dummy tablets if readings are done.

Thephorin (Hoffman-LaRoche) gave excellent results in hay fever, allergic rhinitis and other allergic conditions, say Reynolds and Horton.[512] Gelfand[217] had good results in 59 per cent of twenty-two cases of asthma. Frank[192] relieved eighteen of thirty-one asthmatics (relief only moderate with excellent results in only six; better results in those with seasonal asthma). Criep and Aaron,[138] in seventy-one asthmatics, obtained no relief in 45 per cent, slight in 28 per cent, moderate in 11 per cent, and complete relief in 16 per cent. As with the others, best results were obtained in seasonal cases; they used 25 mg. every four hours. Cohen, Davis and Mowry[121] had good results in forty-two of eighty-three cases of asthma, with less than 50 per cent relief in only twenty-six. Sternberg and Gottes-

man[191] report improvement in nine of twenty-six asthmatics, with failure in thirteen. The statistics of Peters[382] are a bit confusing. In a study of 142 allergic patients, Thephorin controlled the "symptoms of 91 per cent of the patients suffering from both hay fever and asthma." In another paragraph: "Treatment was effective in 75 per cent of all cases of asthma. All the failures occured in bronchial asthma. The drug was 100 per cent effective in pollen and grass asthma."

The place of *Benadryl* (Parke, Davis) in asthma is now fairly well established. It does give some help to milder cases, and is especially good at night because it is an excellent sedative as well. Side reactions, especially somnolence, are common. Blumenthal and Rosenberg[74] obtained good results in two cases of cardiac asthma, but in twelve cases of bronchial asthma Benadryl gave pronounced relief in only one, with moderate relief in three. Fuchs and associates[208] gave 150 to 400 mg. daily to thirty adult asthmatics who had resisted the usual remedies. Symptomatic relief occurred in seven, with recurrence of symptoms when Benadryl was stopped; the drug did not help severe asthmatics nor those with associated infections. Harley[241] and McGavack and associates[319] were not impressed by Benadryl in asthma, and Levy and Seabury[298] found no increase in vital capacity in sixteen patients with extrinsic bronchial asthma, even though six patients said they were better. The subjective evaluation of any drug given asthmatic patients is of little value. There is a strong psychic angle in many of these patients and almost every new form of therapy gives temporary relief if it is presented to the patient from the "right" angle. Benadryl gives only subjective relief in some cases; epinephrine and aminophyllin give both psychic and objective (increased vital capacity) relief. All new drugs, therefore, should be checked objectively as well as subjectively. Pennock[378] also finds results from Benadryl not as striking in asthma as in other allergies; he suggests Benadryl should be tried as a preventive, with epinephrine for acute attacks; and Brewster[82] says that Benadryl is the best treatment for the common "cold;" asthma may thus be prevented.

Lockey[306] dislikes Benadryl in asthma In twenty-one severe intractable patients he gave 100 to 400 mg. per day. Results: no relief in fourteen after taking the drug for three or more days; five patients definitely worse, with death in two; hallucinations and extreme drowsiness in two; improvement in seven, possibly due to sedative action. The two deaths were from asthma, not from the drug, says Lockey, and at autopsy both showed hypertrophy of the right auricles and ventricles. One also had emphysema, chronic bronchitis, pneumonitis, pleuritis, fibrosis and pleural adhesions; the other had marked pulmonary edema, bilateral bronchopneumonia, and a thrombosis of a pulmonary vessel with multiple small infarcts and passive congestion of the liver, and central necrosis and erosion of the terminal portion of the duodenum. One interesting report: Duerfeldt's 65-year-old asthmatic patient survived after taking, by mistake, 50-50 mg. capsules of Benadryl as one dose. A little girl also survived after a stormy course after taking 14 to 16 capsules.[161]

Intravenous administration of Benadryl has been used in asthma and other allergic conditions. Goldman[227] found it of doubtful value in three severe asthmatics. Friedlaender and Friedlaender[198] report: "While reduction in the amount of asthma (nine cases) has been observed in some instances following the administration of 30 to 50 mg. intravenously, the effect has not been consistent enough on repeated administration to warrant its use to the exclusion of such valuable drugs as ephedrine, adrenaline, aminophyllin and iodides In most cases, it has been of definite help through the production of a sedative effect so frequently desired in patients with severe asthma." Rosenberg and Blumenthal[127] have also used Benadryl intravenously in various allergic conditions.

McGavack, Schulman and Boyd[320] found that *Linodryl* (Parke, Davis), another antihistaminic drug, has an action similar to that of Benadryl, but is probably less than half as effective, weight for weight.

Pyribenzamine (Ciba) seems to be used more often than any other of these drugs, at least at the present time. Evidence shows it is not very toxic, and it does relieve edema and pruritus. Henderson and Rose[251] obtained good relief of asthma in ten of twenty-two patients with hay fever and asthma, but the drug only helped three of fifteen chronic asthmatics. Arbesman, Cohen and Osgood[48] found the drug alone helped 41 per cent of twenty-six ragweed-asthma patients, whereas injections of pollen extract relieved 56 per cent. In the discussion of this paper, Chobot said the drug was of little aid in controlling asthma due to pollen—hyposensitization was far superior. In another paper Arbesman reports 47 per cent relief from the drug in 159 asthmatic patients.[37]

Antergan (Phenyl analogue of Pyribenzamine, Ciba) combined with atropine, was successfully used in asthma and angioneurotic edema by Danielopolu and Rosenzweig.[141] Serafini[460,461] says that this drug gave complete symptomatic relief in four of nine cases of extrinsic asthma and in eight of thirty-six of the intrinsic type, with partial relief in three and thirteen, respectively.

Antasten, another histamine antagonist not used in the United States, did not help asthma nor migraine sufferers, says Kallos.[275] *Chlorothen* (Lederle) was tried in fifty-four asthmatics by Feinberg,[150] with satisfactory relief in only one; six of twenty patients with an allergic cough were helped. The drug helped the hay fever symptoms but not the asthma in twenty-five of forty-seven patients.

A number of papers compare the various antihistaminic drugs. Marsh[333] discusses them in general and has a nice table giving the name of each, the chemical structure, how dispensed, with a comment on each. Criep[126] found little value in asthma from Benadryl, Pyribenzamine, Thephorin, and Thenylene; they could not prevent onset of asthma in pollen cases nor alleviate the asthmatic symptoms. Their use in no way replaces the need for a careful study and adequate therapy from the allergic point of view. Bernstein, Rose and Feinberg[60] also obtained poor results in asthma from Benadryl, Pyribenzamine and Neo-Antergan. Arbesman[36] found relief in asthma: 45 per cent from Pyribenzamine, 43 per cent Neo-Antergan, 33 per cent Neohetramine, and 36 per cent Antistine. *Hydryllin*, on the other hand, contains aminophyllin as well as Benadryl, and gave 64 per cent relief in forty-eight patients with inhalant asthma; but even this combination was not as effective as epinephrine, ephedrine or larger amounts of aminophyllin.

Neither Pyribenzamine nor Benadryl helped asthmatic patients of Engelsher,[174] and only gave partial relief in ten of twenty asthmatic cases of Loveless and Brown[316] and Loveless.[315] Logan[312] found both drugs of some use in asthma in children. Kleckner[250] obtained great relief in six of twelve cases of seasonal asthma, with improvement in five others (with Benadryl), but Pyribenzamine gave good results in only one of twelve cases, with lesser improvement in nine others. He also tried Anthallan in ten cases with even poorer results (improvement in only six cases).

Hartman[218] has an excellent review of the histamine theory and the role of antihistaminic drugs. The effects of histamine are evidently *not* the complete explanation for allergic disorders. Clinically, Benadryl and Pyribenzamine help pollen asthma in 45 per cent, 30 per cent in perennial asthma, and almost none in asthmatic attacks precipitated by infections. Hartman found that a new drug, Compound 887, helped 80 per cent of ninety asthmatics, in sharp contrast to Benadryl and Pyribenzamine. The new drug experimentally is about twenty times as potent as papaverine and about one-fifth as effective as epinephrine in relaxing histamine-induced bronchospasm.

Spain and Pflum,[484] in 1,418 cases of bronchial asthma, report improvement in about 35 per cent of cases; Pyribenzamine, Benadryl, Hydryllin, Trimeton, and Neo-Antergan were given as symptoms arose, not continuously; unpleasant side effects were frequent. Waldbott[542,543,541] found that the new RP3277 gave longer relief than Antistine, Neo-Antergan, Neohetramine, Trimeton, Benadryl and Pyribenzamine. Relief in asthma was obtained in from 6 per cent (Antistine) to 34 per cent (Neo-Antergan), with the others in between. Weiss and Howard[556] confirm the fact that these drugs do not prevent the development of seasonal asthma. None of the patients who had been given preseasonal or perennial hyposensitization developed asthma while under treatment, whereas ten hay fever sufferers, not injected, developed asthma; three of these were taking antihistaminic drugs when asthma began. The incidence of asthma in non-hyposensitized patients was 10.3 per cent—a strong argument for hyposensitization.

Norén and Feinberg[362] report that aerosols of fourteen different antihistaminic drugs prevented aerosol-induced histamine-bronchospasm in guinea pigs, although the duration of action of the aerosol averaged only one hour, several hours less than that from injections of these drugs. The method is useful in assaying the antihistaminic potency of drugs, although such assay does not necessarily refer to antiallergic potency. Commenting on this article Abramson[1] states "It has been pointed out that bronchospasms produced by histamine are relieved by the antihistaminic drugs; this is not true of bronchospasm produced by pollen aerosols. Bronchospasms produced by pollen aerosols in allergic individuals are readily removed by epinephrine aerosols. Contrary to the point of view of the authors, the editor believes that these experiments on the antihistaminic action, are, in all likelihood, unrelated to the clinical effectiveness of antihistaminic drugs in the allergic state."

General reviews of antihistaminic principles and therapy are also reported by Friedlaender and Friedlaender,[197] Feinberg,[175] Léger,[202] Loew,[310] Rodriguez Candela,[424] Piness,[356] Arner,[575] Alonso, Adams, et al,[19] Herxheimer[255] and by a note on antihistaminic drugs.[24]

[From this survey of the literature we must conclude, as we did in our last review, that these drugs are only mildly effective in bronchial asthma. They are not nearly as potent in asthma as are the time-honored epinephrine, aminophyllin, ephedrine and iodides, and probably one or two of the newer epinephrine-like drugs such as Isuprel. In hay fever the main danger from the use of these drugs as a substitute for hyposensitization is the frequent occurrence of asthma. This complication is rare if hyposensitization is properly carried out. Aerosol and intravenous antihistaminic therapy are still in the experimental stage. The new drug 3277RP will bear watching. In status asthmaticus a nightly dose of Hydryllin or Benadryl may be helpful, perhaps chiefly because of their sedative effect.]

OTHER DRUGS IN TREATMENT OF ASTHMA

Aminophyllin is the best drug in the treatment of status asthmaticus and, in adults, it often gives better results than epinephrine for single attacks of asthma. We inject it in the office and at the home; in the hospital we use it in 10 c.c. vials, and, mixed with 5 per cent glucose, either intermittently or continuously. We also use it rectally in suppositories or dissolved in water. It is less efficient by mouth because of frequent nausea. Wyrens[564] agrees with the above statements, and Franklin[193] uses rectal suppositories, each containing 0.5 gm. aminophyllin, 0.1 gm. sodium pentobarbital, and 0.06 gm. benzocain, with half-strength for children. He obtained good to marked relief in 69 per cent of adults and 94 per cent children. Tolerance to aminophyllin after long use occurred in 20 per cent of the sixty-five adults, and in 10 per cent of the adults side effects occurred, e.g. weakness, nausea, diarrhea and rectal irritation. [Rectal irritation may be due to the benzocain, a notorious cause of contact dermatitis.] Aminophyllin is especially good in epinephrine-fast patients.

A colorometric method for quantitative estimation of theophyllin in the blood is reported by Truitt et al[515]. Samples of blood with known added amounts of theophyllin (0.2 to 0.8 mg. per cent) were analyzed with very minor errors. Blood levels of eight patients receiving 1 to 2 gms. theophyllin sodium aminoacetate daily ranged from 0.23 to 1.8 mg. per cent. Plummer[385] also assayed theophyllin in the blood and urine. There was no interference from caffein, theobromin, uric acid, ethylenediamin or sodium acetate. The analysis is sensitive to 0.13 mg. anhydrous theophyllin per 100 c.c. of blood or urine. In dogs injected intravenously the thirty minute blood level was about half that found five minutes after injection (8 mg. per Kg.); at sixty minutes about one-third; at ninety minutes theophyllin could not be detected in the blood in four of the five dogs. During this period 1.8 per cent of the injected theophyllin appeared in the urine.

Thousands of intravenous injections of aminophyllin have been safely given to patients with bronchial asthma, with practically no trouble if the solution is injected slowly. It is remarkable that fatalities have only been reported in patients with cardiac disease, first by Merrill (JAMA 123:1115, 1944; 124:250, 1944), and more recently by Bresnick, Woodard and Sageman.[51] Fatalities occurred suddenly in three acutely ill patients, two with coronary occlusions, and the third with uremia, myocardial damage, and acute pulmonary edema. The mode of death suggested cardiac standstill or ventricular fibrillation. The authors say that aminophyllin, in addition to its action as a coronary vasodilator, stimulates the myocardium. The increased cardiac action may be greater than can be compensated for by the vasodilating effect of the drugs, with resultant coronary insufficiency. Hyman (JAMA 136: March 27, 1948), in discussing this paper says: "Never give an intravenous injection when a drug can be given effectively by any other route," he then urges 26 to 28 gauge needles and great caution and slowness in injections. "Speed shock," he says, is probably frequent and deaths probably occur and are not reported. In another letter, Deshmukh, from India (JAMA 138:527, 1948) thinks Hyman is wrong; speed is not the cause of death, he says, although one should not inject too rapidly. The drug itself is the cause, or perhaps death is due to a reflex inhibition of the heart caused by pricking the skin. Stahl[490] also warns of the danger in cardiac disease from intravenous aminophyllin. [From all this there emerges the fact that *death in bronchial asthma has not been reported* when aminophyllin has been injected intravenously; deaths, of course, may have occurred but were not reported].

Epinephrine, if used over long periods of time, can cause an "autonomous anxiety state," says Cameron,[100] with head and neck aches, increased cardiovascular activity,

and such venous phenomena as blanching of the veins and the appearance of "goose pimples" over the course of the veins. [We have recently had two cases of undoubted hyperthyroidism which were caused by excessive use of ephedrine and epinephrine 1:100 sprays; even the thyroid glands were enlarged. One went into shock, the other did not reach this stage. Substitution of aminophyllin and iodides brought prompt relief].

Benson and Perlman,[57] in the past ten years, found forty-eight known dead in 648 patients who used 1:100 epinephrine (or similar drugs) by inhalation; these were part of a total of 2,236 asthmatic patients. During this time death occurred in only twenty-two of the 1,588 patients who did not use the spray; therefore, they state, the injudicious use of this spray has contributed materially to death from asthma. They give three case reports, with autopsy findings. Commenting on the conclusion of the authors, Abramson agrees that the injudicious and unskilled use of epinephrine in any form is contraindicated in asthma; one must, however, teach the patient how to use the aerosol; furthermore, only the more severe asthmatic patients are apt to require epinephrine aerosol. Barach also takes issue with the authors and says "In my experience nebulized epinephrine produced by a nebulizer that creates an aerosol of small particle size is one of the most valuable therapeutic agents in the management of bronchial asthma." Segal also disagrees with Benson and Perlman (J. Allergy 19:278-9, 1948). In replying (page 279), Benson and Perlman emphasize that in the Pacific Northwest the purchase and use of aerosol epinephrine is frequently without medical supervision and the drug is therefore often used to excess. The Council on Pharmacy and Chemistry[133] strongly condemns the vicious method of selling Allergasol (Chemtronic Laboratories), a racemic epinephrine; the physician is used as the dupe to obtain the names and addresses of his asthmatic patients; then the product is sold directly to the patient and used by him without supervision.

Rowe and Rowe[131] report local cutaneous allergy (Arthus phenomenon). Erythematous nodules with resultant necrosis occurred in four asthmatic patients who used epinephrine for over 6 years. Two of these were able to use synthetic epinephrine with little or no trouble (the substitute was not tried in the other two patients).

Constitutional reactions can also occur from epinephrine. Mattioli[295] reports myocardial infarction in two cases, with death in one; in both cases the epinephrine was given because of malaria. The author says the drug is innocuous in persons with a perfectly normal heart. But signs of arteriosclerosis may always be expected in persons over forty-five, especially if, in addition, they have chronic malaria or other debilitating diseases. Seltzer[161] states that only rarely does a severe reaction follow epinephrine; when reaction occurs it is usually an exaggerated pharmacologic action of the drug. In his 26-year-old patient with asthma, however, convulsions occurred ten minutes after an injection of 5 drops of 1:1000 epinephrine. The spasms lasted thirty minutes and resembled those due to tetanus or strychnine poisoning. The patient was able to return home by himself after an hour and was entirely well the next day. Later, "convulsive seizures could be reproduced in this individual by subcutaneous injections of 1:1000 epinephrine in amounts over 5 minims. It was noted that it was easier to produce a convulsion after he had taken a dose of ephedrine, and in view of the augmentative effect of ephedrine on the action of epinephrine this seems quite logical." Later, the patient said he had two previous convulsions after epinephrine, one after an injection, the other after excessive use of nebulized 1:100 epinephrine. The author felt that the convulsions were due to hyperventilation tetany produced by the stimulating effect of this drug on the patient's central nervous system. [We question the wisdom of reproducing convulsions in this patient; such spasms cannot be harmless].

Hanzlik,[242] as quoted by Glaser (Ann. Allergy 6:193, 1948), says serious accidents from overdosage of epinephrine are uncommon, but may occur from injections and from aerosol especially in countries which use stronger solutions than the 1:100 which most of us advise. Hanzlik calls attention to an important article by Möller on the treatment of acute epinephrine poisoning (Acta med. Scandinav. 110:361, 1942). Möller's patient, a 12-year-old girl weighing 34 Kg., accidentally received 20 c.c. of 1:1000 epinephrine, i.e., double the known fatal dose for a male adult. Nausea and vomiting and a barely palpable pulse followed, with extreme pallor and cold extremities, with coma in forty minutes. Inhalation of four ampules of amyl nitrite restored consciousness; this was followed by 3 mg. nitroglycerin in one and one-fourth hours, then erythrol tetranitrate 5 mg. by mouth, then three intravenous injections of 5 mg. each ten minutes apart; five minutes later another 5 mg. intravenously (total of 25 mg. within 100 minutes after the accident). Two hours after the almost fatal injection of epinephrine the face was pink but the legs were still cold and pale, and the blood pressure was low. Recovery was due, says Möller, to

the persistent use of nitrites: peripheral vasodilators, known antagonists of epinephrine. Glaser adds that a tourniquet above the site of epinephrine injection with release at intervals might have helped, just as it does with reactions from allergens.

Butanefrin (Ethyl-Nor-Epinephrine, Winthrop) gives increased vital capacity just as do epinephrine and aminophyllin, say Levy and Seabury.[209] Its chief value in asthma is the absence of the undesirable pressor side effects so frequently found with epinephrine. In ten patients with moderately severe asthma, 2 mg. gave uniform increase of vital capacity, reserve air, complemental air, expiratory differential, increase in volume of minute ventilation, and a tendency to return to the initial volume one hour after the drug was given. The heart rate increased, and the diastolic blood pressure was lowered. Eight patients obtained complete symptomatic and objective relief; the other two required additional medication.

Nethaphyl (a combination of Nethamin Hydrochloride and Butaphyllamin, Merrell) was given to 750 patients with allergic bronchitis and bronchial asthma. There were 150 children, and most of the patients also had nasal allergy. The results were about those obtained from other theophyllin compounds. Side effects were minimal. The average optimum dose for children was ⅜ grain Nethamin and ½ grain Butaphyllin; the adult dose was double, and the drug was given every 3 to 4 hours, as necessary (Hansel,[241]).

Procaine is advocated by Donoso and his co-workers;[155] the drug is supposed to do away with the engorgement of the lesser circle of the lungs as pointed out by Jiménez Diaz and his associates. They gave 10 c.c. (1 per cent) procaine intravenously in forty-five attacks of asthma, with relief in 10 to 15 minutes. In one case 10 c.c. was injected daily for ten days, followed by longer periods. Urticaria occurred in one case. (The drug also lessened dyspnea in patients with pulmonary infarcts, emphysema, pulmonary sclerosis, and cardiac asthma). The literature on procaine in asthma is cited together with a warning about danger from the drug; Waldbott had a near fatality from an injection of 0.5 gm. given by another physician.[71]

Khellin, as noted in our last review,[321] gave promising results in asthma. In an answer to a query[22] the drug and literature are described, with a note in Lancet May 17, 1947, page 682: "That khellin may have further uses is suggested by the observation that after a single intramuscular injection of 200 to 300 mg. complete and prolonged relief was obtained in forty-one of forty-five patients with severe bronchial asthma; and even this fairly large dose had no effect upon the blood pressure. It has, moreover, relieved attacks resistant to adrenaline and aminophyllin. Whether, as suggested, khellin is safer than aminophyllin is not certain, for experience with it is so far small. If, however, khellin is to come into general use preparations of it must be purified and standardized, for there is some evidence that the impurities in Amni visnaga may be toxic."

Sodium Ascorbate is recommended by Ruskin[136] for the treatment of asthma and other allergic conditions. The recommended dosages of Vitamin C are 1000-2000 mg. daily. It is definitely antihistaminic, says Ruskin. The sodium ascorbate is more effective than ascorbic acid. *Digitalis* is recommended in patients with asthma if cardiac decompensation is associated.[30] "The normal heart can tolerate many years of severe asthma without signs of decompensation." Rosillo[128] has successfully used 5 per cent Magnesium sulfate intravenously in all forms of chronic asthma. [We tried this many years ago but abandoned its use as inefficient]. Loeper[308] gave a series of ten intravenous injections of *cinchofen* (0.50 gm. diluted in 200 c.c. dextrose solution); complete cessation of asthmatic symptoms occurred in an unexpressed number of chronic patients, enabling them to continue their usual way of living under maintenance treatment of the same drug by mouth. [One should mention the danger of liver damage from cinchofen].

Brown[57] gave 10 c.c. intravenous injections daily for ten days; he used the respiratory enzyme *cytochrome C*. Five patients were tried with good results in one with bronchitis and emphysema and in another with coronary heart disease; fair results in a patient with chronic bronchitis, and no results in two patients with inhalant sensitivities with or without infection. The respiratory enzyme may lessen dyspnea by causing faster absorption of oxygen from inspired air. As mentioned previously,[247] Hartman found that a new synthetic antispasmodic known as *Compound 887* (Searle), in doses of 0.2 gm. at bedtime, gave symtomatic relief to about 80 per cent of ninety patients with nocturnal dyspnea. No toxicity was noted, nor habituation or loss of tolerance. It increased vital capacity. *Pneumodan* (parasulfamidobenzoic acid) is recommended;[283] it is said to be an efficient antispasmodic, cardiotonic, diuretic, and central depressant.

Morphine continues to be used for asthma, but, fortunately, much less frequently and with much greater caution. Katz and Chandler[277] have an excellent paper on morphine sensitivity in kyphoscoliosis. Morphine may aggravate symptoms in patients suffering from such diseases as mechanical obstruction in the bronchial tree, bronchial asthma, and myxedema. In addition, the authors point out the serious consequences which resulted when morphine was given two patients with both kyphoscoliosis and heart failure. The first patient was very restless and was given 10 mg. morphine subcutaneously; in fifteen minutes the respirations diminished to two per minute and, despite stimulation, death occurred in twelve hours. The second patient almost died after 10 mg. morphine; within an hour coma occurred, with a respiratory rate of five; oxygen, caffein and coramin revived her. Three days lated 4 mg. morphine was tried, and for two hours the respiration declined from twenty-six to sixteen per minute and became Cheynes-Stokes in character. The authors point out that in kyphoscoliosis [unlike early bronchial asthma] the depth of respiration is maximal and fixed, and the effect of a lower respiratory rate induced by morphine can only be one of increased anoxia.

Ballantine[16] occasionally uses morphine but warns of its danger; he prefers codeine, especially for troublesome cough. Powers[391] likes *Demerol* for sedation, analgesia and spasmolysis. In asthma he often combines it with epinephrine in the same syringe (about 30 to 50 mg. Demerol and 0.2 to 0.3 c.c. epinephrine). Addiction is uncommon but can occur. Rudner[434] reports that *Hycodan bitartrate* is an effective and satisfactory drug for the cough of chronic pulmonary diseases. He used it in fifty cases, chiefly tuberculosis (no cases of bronchial asthma).

Sensitivity to *iodides* occurs occasionally and the drug must be stopped. Huff[267] gave sodium iodide for a cough. After the second teaspoonful severe aching of the breasts occurred, followed by acute mastitis. The teeth and gums were very tender, and severe headache ensued. Symptoms persisted for two days, despite Benadryl, epinephrine, and withdrawal of the iodides.

Ethylene Disulfonate continues to be used. Wasson[553] first forbids many foods, all drugs, tobacco and alcohol, then gives the drug. He reports 80 to 100 per cent good results in fifty-two of ninety-five patients with bronchial asthma, with improvement in another twenty-six patients. Bodman and Felix[75] gave an average of 3.2 injections to 152 adults and eight children over a period of 12 to 48 months. Satisfactory results are claimed in 82.4 per cent of the patients with asthma. Bartlett,[52] over a period of six years, obtained complete relief in 391 of 725 cases of bronchial asthma, (54 per cent), with excellent results in another 225 patients (31 per cent); no relief in only 15 per cent. Against these three papers which claim such good results are the statements noted in previous reviews, e.g., that of the Council of Pharmacy and Chemistry (JAMA, 131:1495, 1946) and that of Archibald (Arch. Pediat., 62:219, 1945), who say the drug is practically worthless. There is also an answer to a query.[29]

PENICILLIN AND AEROSOL THERAPY IN ASTHMA AND RELATED CONDITIONS

A large number of papers deal with the use of penicillin both by injection and by aerosol, and there are papers using other drugs by aerosol.

Penicillin, of course, is indicated in the treatment of many infections, with or without the presence of asthma. The question of whether penicillin should be injected or inhaled has not been settled, nor do we as yet know whether we should inject penicillin every three hours or use it in depot fashion once or twice a day or less often.

Crystallin penicillin by injection is advocated by Sterling and his associates[492]; they gave it intramuscularly in fifteen patients with chronic bronchial asthma in whom allergic and other measures had failed. They gave 100,000 units every three hours the first day, then 25,000, 50,000 and 100,000 again for a total of 5 million units in eight days. They obtained excellent results in three cases, good in four, fair in one, with failure in four; in three cases injections were stopped because of severe reactions. The authors urge massive dosage in intrinsic chronic bronchial asthma. Gay and Marriott[215] injected 600,000 units of penicillin in wax and oil in thirty-nine cases of "bacterial" asthma (daily injections for ten days). Each patient then received a booster dose of 600,000 units every 5 to 7 days to prevent recurrence of infection. Good results were obtained in nineteen of twenty-two private patients and in twelve of seventeen patients in the outpatient department. The authors praise the booster injections. Miller[347] injected 12,500 to 25,000 units at three-hour intervals to twenty-nine patients with intractable asthma; average total dosage was 1,300,000 units. Symptoms during treatment disappeared in eleven cases; of these, seven experienced acute exacerbations 1 to 12 months later; in four, exacerbations recurred

after retreatment. Improvement occurred in eleven patients, five continued to show improvement, six relapsed when the injections were stopped. There was no improvement in seven. Over-all results in the twenty-nine patients showed four well for over a year, a transient recurrence in one, nine improved but not symptom-free, and fifteen unimproved. Penicillin is therefore not a panacea in intrinsic asthma but it is worth while in bacterial asthma. Bauman et al[54] continue to report favorable results from the use of buffered *oral* penicillin. They now use 50,000 units per dose for children and 100,000 units for adults, and repeat this every four hours day and night for five days. Pneumococci and streptococci usually disappeared from the nose. The study comprised sixty children and fifteen adults. There were fewer respiratory infections after penicillin.

Penicillin aerosol has become popular, both in liquid form and as a dust. Hagens, Karp and Farmer[229] state that while penicillin aerosol was helpful in bronchiectasis, another antibiotic was necessary to eliminate the Gram-negative, penicillin-resistant bacteria. They treated 10 patients with combined penicillin-streptomycin aerosol and 111 with penicillin aerosol alone. Bronchial asthma was present in four of the first group. The aerosol was given by an oronasal mask, a DeVilbiss No. 40 nebulizer, and an oxygen tank. Sixteen inhalations were given per twenty-four hours, with 1.5 c.c. per inhalation. All but one patient received penicillin alone for several days, then the combined aerosol for 3 to 9 days. 200,000 units of penicillin daily eliminated Gram-positive organisms from the sputum, 500,000 units of streptomycin daily the Gram-negative bacteria. Improvement occurred in nine of the ten cases, but results were not as good in those with asthma as in bronchiectasis. Of the 111 who received penicillin aerosol (fifteen different pulmonary conditions), only seven failed to show some improvement. Apparent cure occurred chiefly in patients with acute localized infections of the upper respiratory tract. Inhalation of penicillin dust also gave good results, as reported by Krasno, Karp and Rhoads.[258] They used a mask and crystallin sodium penicillin processed to #50-100 mesh particles. A series of fifty-five patients with upper respiratory infections, forty-six with common colds and nine with lower respiratory infections were studied. Each received 100,000 units of penicillin dust for twenty minutes three times daily. Gram-positive and some Gram-negative bacteria rapidly disappeared. One case of bronchial asthma was greatly improved, with moderate improvement in patients with bronchiectasis and chronic bronchitis. About 75 per cent of patients with acute upper respiratory infections cleared with only one treatment. The article contains a picture of the apparatus and tables of results, with assays of the blood.

Segal, Levinson and Miller[155] have a nice article on penicillin inhalation therapy in respiratory infections. They used liquid penicillin with a Vaponefrin nebulizer and oxygen. The method is advised for patients with purulent sinusitis, bronchiectasis, pulmonary abscess, infections of the lungs with streptococci or staphylococci or with penicillin-susceptible stains of Friedlaender's bacillus, acute tracheobronchial edema, and infections secondary to underlying primary disease of the lungs, such as emphysema, cysts and infarcts. As regards infective asthma, the results in twenty-two patients were "generally disappointing," although striking improvement was occasionally observed. Most patients, however, were able to raise sputum more easily, although many objected to the taste and irritation of the aerosol. Local and/or generalized reactions can occur. Mild bronchial asthma occurred for the first time in two patients receiving the aerosol for chronic bronchitis and emphysema and in two with bronchiectasis, with prompt relief when epinephrine was substituted for the penicillin.

Finke[185] continues to stress the prevention of bronchitis and bronchiectasis. Penicillin aerosol is excellent in respiratory infections, especially in "asthmatic bronchitis" in children and young adults. To Finke the symptoms in his patients begin as chronic bronchitis with asthma as one of many symptoms, and, of course, removal of infection clears the "asthma" as well. This infectious asthma is entirely different from asthma due to allergy.

Cintra[114] treated eighty-eight patients with infectious respiratory disease with inhalations of penicillin (100,000 units four times daily—the last followed by an injection of 300,000 units in wax and oil). Streptomycin was added if Gram-negative bacteria predominated in the sputum. When allergy was also present, desensitization, with or without autovaccines, was carried out. Results noted in forty-three patients with bronchial asthma observed one and two years after treatment was stopped: clinical cure in eight, great improvement in twenty-four with periodic asthma, and improvement in six with acute asthma with frequent crises, and in five cases of status asthmaticus. Good results were also obtained in bronchitis and sinusitis. Dumm[157] prefers aerosol to injections, but in asthmatics nebulized epineph-

rine or aminophyllin should precede the use of penicillin aerosol. Ruiz Moreno and Bachman[135] in fifty cases of asthma with non-tuberculous infection, found aerosol penicillin of real value; but it is of no value in asthma without infection. The benefits are transient.

Bryson and Grace[93] successfully used liquid penicillin aerosol in fifty cases of respiratory infection. They used Zephiran 1:1000 aqueous solution as the solvent. Before each treatment the patient inhaled 0.5 c.c. of the 0.25 per cent solution of Neo-Synephrine, and penicillin was also given intramuscularly. In one severe asthmatic there was only one attack during the eighteen months after treatment. Taplin and Bryan[504] used dry micronized powders with a particle size of about 1 micron. They used a combination of penicillin, glucose and Benadryl. Favorable results were obtained in respiratory infections. In fifty-one cases of chronic asthmatic bronchitis and related pulmonary diseases, sensitive organisms quickly disappeared, cough and sputum were lessened, and the asthma was frequently relieved. The technique is simple. Abramson[2] prefers the liquid aerosol to the penicillin dust used by Taplin and Bryan; he discusses the physics of aerosolization.

Prigal and his associates, in a series of articles,[397,398,399,400,401] re-emphasize the usefulness of steam-generated aerosols of penicillin in the treatment of infections, with or without associated allergies. They use propylene glycol as the solvent. In a total of sixty-one patients with asthma and associated infection, forty were treated with a breathing box. All nine with mild asthma cleared promptly; immediate improvement occurred also in seventeen of twenty-one patients with moderate asthma; four of ten severe cases were relieved by inhalations of epinephrine or aminophyllin. The tent method was used in six cases of relatively severe asthma, with relief in four. The chamber method was used in three, with good results in two. The open method was used in twelve hospitalized patients with status asthmaticus, following preliminary inhalation of aminophyllin. Inhalation was also carried out with ammonium chloride and sodium sulfadiazine in some cases, as well as penicillin. Fairly good, though temporary, results were obtained in eleven of the twelve. Improvement also followed aerosol therapy in upper respiratory infections associated with nasal allergy. Prigal and his associates found good penicillin levels in the blood. Penicillin dissolves readily in propylene glycol to form an effective, stable aerosol; the addition of 5 per cent glycerin further stabilizes the aerosol.

Garthwaite and Barach[214] used aerosol penicillin in preference to the intramuscular route because the concentration in the sputum is obviously higher in the former. They obtained marked improvement in fifteen of fifty-nine courses of therapy in thirty-five patients with bronchiectasis, with moderate relief in twenty-two; good results were also found in other respiratory infections. Dwyer[168] treats "colds" and upper respiratory infections by penicillin aerosol. He says "some objections have been raised about treating the common respiratory infections with penicillin on account of rendering the organisms resistant. If enough penicillin is used, the organisms are entirely eliminated, which overcomes this objection." Davis[147] uses 50,000 to 100,000 units of penicillin alone or combined with an equal amount of streptomycin. Patients with infection plus nasal allergy and/or asthma were helped; those without infection were not relieved. Veach[531] also likes combined penicillin and streptomycin aerosol; Berre,[62] prefers Isuprel (Aleudrin) aerosol, with or without atropine; Koelsche[284] obtained temporary relief from aerosols of penicillin, streptomycin, Neo-Synephrine, epinephrine, ammonium chloride, and aminophyllin; and Abramson[6] discusses the possible value of inhaling Vitamin C with or without other agents. Burrage's paper[99] is a review of therapy in allergy. He likes inhalations of epinephrine, Isuprel, 1 per cent Neo-Synephrine and penicillin. Mallet[330] also discusses aerosols in asthma; the optimal size of particles is 0.5 to 5 microns in diameter; he likes theophyllin or aminophyllin with sodium benzoate and water; penicillin is added if infection is associated (150,000-200,000 units daily for ten days); results are variable. Bubert and Cook[94] combined Theoglycinate (theophyllin and sodium glycinate) with penicillin in aerosol in the treatment of thirty-three cases of severe bronchial asthma. The procedure is safe and effective and has frequently been successful when conventional therapy has failed. The authors feel that acute infection is usually present in status asthmaticus or in the more severe cases of asthma that do not reach this level of severity. One must combat the infection as well as any underlying allergic factor. The aerosol was administered in a small transparent canopy with oxygen or an oxygen-helium mixture for nebulization. A 5 per cent solution of theoglycinate aerosol was usually used, about 2 c.c. every four hours preceding the penicillin aerosol. For severe dyspnea continuous aerosol of 5 per cent theoglycinate has been used for twelve and one-half hours and 10 per cent for six hours, with considerable benefit and no harm. The penicillin aerosol which followed usually contained

20,000 units with a maximum of 50,000 units every three hours. Aerosols of streptomycin and sodium sulfadiazine have also been tried with or in place of penicillin.

Harsh[240] has a nice study of commercial nebulizers. In fifty-nine samples representing fifteen brands there was a 49-fold variation in the amount delivered by one squeeze of the hand bulb. No one model is best for all purposes. Certain samples emitted droplets and were not suitable for oxygen at eight liters per minute nor for compressed air at forty pounds per square inch. Harsh also gives the formulae of certain commercial and non-commercial epinephrine solutions. Failure usually indicates a poor nebulizer. The addition of glycerin helps because it stabilizes the mist, reduces irritation, and retards absorption; it has other helpful properties. In testing, he used gentian violet, a glass slide, and an ocular micrometer. Sloan and his associates[475] also tested the efficiency of commercial nebulizers; they used mice and rats, and state that the amount of nebulized substance which reaches the trachea, bronchi and bronchioles is not sufficient therapeutically. This finding is especially important as regards penicillin aerosol.

Tiffenau and Singuier[511] were able to delay absorption of penicillin, epinephrine, atropine and Aleudrin by adding a 3.5 per cent aqueous solution of Subtosan. The tests were made in fifty asthmatic patients, and in 50 per cent of the cases the delayed absorption resulted in prolonged relaxation of the bronchial tree; the systemic side effects of epinephrine and ephedrine were decreased. Segal, Levinson and Beakey[451] describe a mechanical demand valve to be used with a nebulizer and face mask for the automatic administration of antibiotic aerosols.

MISCELLANEOUS MEASURES IN THERAPY

The great value of bronchoscopy in diagnosis and in treatment has already been discussed. Irigoya Freyre[269] found bronchoscopic suction very helpful in the treatment of 168 patients with status asthmaticus, with only three failures; he also instilled, topically, 5 per cent silver nitrate. Reiser and Ferris[409] used anesthesia and the Drinker respirator for artificial respiration in three patients with acute intractable asthma, with prompt and satisfactory relief of the anoxemia. One patient was treated early in the course of the attack and eventually recovered. Although the other two died the procedure did give temporary and excellent relief. The maneuver should be used early as an adjunct to the usual therapy. *Pneumoperitoneum* was used successfully in a 45-year-old female asthmatic emphysematous patient of Rubin and Glass.[423] After the air was injected the dyspnea was lessened and the improvement has continued for four months during which period the pneumoperitoneum has been maintained by repeated injections of air. There was some pain in the shoulders and fever for several days after the first injection.

Climatotherapy: Stevenson[496] tells us that the southern third of Arizona is less than 2500 feet above sea level, sunny and warm, and has meager rain and low humidity; the barometric pressure is relatively stable with few storms. The climate is rather even with only slight variations, and while seasonal changes occur they are not disturbing. Residence in this section should therefore benefit patients with (a) diseases helped by sunshine, e.g., visceral and bone tuberculosis and lupus vulgaris; (b) respiratory diseases, e.g., pulmonary tuberculosis, sinusitis, chronic bronchitis, bronchiectasis and bronchial asthma; (c) rheumatic and arthritic diseases; (d) infections of the upper respiratory tract. Those with asthma aggravated by infections and changes of weather are usually better after months or years in Arizona. Those with chronic bronchitis are also helped, and even those with bronchiectasis usually feel better because there are fewer respiratory infections. The climate of the northern two-thirds of Arizona is also pleasant but not as stable. Schutzbank[446] also notes improvement on moving to Tucson, Arizona, based on a study of 100 consecutive allergic patients observed for a year or more unless improved before that time. But he does not give the climate the entire credit; part of the improvement is undoubtedly due to lessening of exposure to certain allergens, e.g. pollen or animal, part to nervous or psychic factors. The foliage in Tucson is quite different from that of the East or Middle West, and therefore some lose their pollen hay fever and/or asthma. A few, however, develop symptoms because of greater exposure to Bermuda grass pollen. To obtain best results especially in infectious cases, patients should stay in Arizona for at least a year. Penicillin by injection or aerosol was helpful in seventy-five patients, and the benefits were frequently maintained in this climate because infectious diseases are much less frequent. Of the 100 allergic patients, 76 per cent were helped. Of sixty-seven asthmatic persons, fifty-one were completely relieved or more than 50 per cent benefited. In these fifty-one good results, avoidance of psychosomatic influences seemed very important in twenty, lessening of respiratory infections in nineteen, escape from a specific allergen in six, with six undetermined. Five of the sixteen asthmatic

failures occurred because of failure in determining or relieving a psychic cause; in eight, severe chronic respiratory infections were present, e.g., sinusitis, bronchitis or bronchiectasis, not amenable to treatment. Furstenberg[210] has a nice article on this subject; he spent many months in Arizona and analyzed replies from ten physicians who live in that area. The replies varied from enthusiastic to pessimistic, but all agreed that infections asthma was usually benefited. The role of psychosomatic factors is exceedingly important, and if a patient is plagued by his wife and comes by himself to Arizona he is apt to do well; if he brings his wife along his asthma is apt to continue. The replies warn indigent patients to stay away from Arizona; conditions there are just too difficult for poor people. Furstenberg suggests that a scientific project should be started. Several hundred patients with asthma, other allergic diseases, arthritis, and sinusitis should be sent to the Southwest and closely watched to see if they actually are helped by the climate.

Egbert[171] says that when patients with severe bronchial asthma with much mucus move from humid to dry atmospheres they may become so dry in twenty-four to seventy-two hours that treatment is needed to increase the flow of mucus. Severe dry asthma may take the place of moist asthma. Many patients, however, are helped. In a study of 188 asthmatics seen at the Selective Center for climatic therapy of the Lyon (France) University Medical School, it was found that climatotherapy (especially at LeMont Dore and LaBourboule) gave best results in non-infections asthma and in cases treated early. Vital capacity and fewer spells the following winter were found in all cases. Best results were obtained in patients who visited these resorts for three weeks each of three successive years (Delore et al[343]).

X-ray and radium therapy continues fairly popular in asthma and allergic rhinitis. MacInnis[327] notes that x-ray treatments reduce the size of tracheobronchial lymph nodes and decrease mucus secretion. They also have an effect on the circulation of hormones, liberation of antibodies, desensitization of body to proteins, stimulating effect on the production of eosinophiles, and complex influences on the whole body. In four asthmatic children relief from attacks for at least six months occurred in three. The relief is temporary. The sinuses and mediastinum were exposed to x-ray at five-day intervals for four treatments (50 r each exposure). Van Vaerenberg[531] helped forty-three asthmatic patients in Belgium with small roentgen ray doses (75 to 100 r) to the spleen and hilar and cervical nodes. From France, Vallery-Radot and Blamoutier[530] used x-ray therapy in 1000 cases of asthma. Of the 680 with sufficient follow-up, perfect results were obtained in 23 per cent and good in 18 per cent. The exposure was chiefly to the chest. The authors state that "results may be expected in any type of asthma, except in allergic asthma" [This last remark is confusing; what kind of patients received x-ray treatment?].

Radium to the nasopharynx, originally used to lessen deafness, continues to be tried in children with asthma and allergic rhinitis. The good report of Ward, Livingston and Moffat[551] is the same as noted in our last review.[521] Pool, Harrill and Rousseau[390] used roentgen nasal therapy in twenty patients with asthma, with good relief in three; the authors conclude that more cases must be studied before the real value of irradiation can be determined, but the method does warrant further study.

Shock treatment of asthma by *insulin* gave excellent results in thirteen cases, says D'Arcangelo Domenico,[145] with relief in thirty to sixty minutes. In 25 per cent the asthma disappeared completely, was lessened in 25 per cent, and no permanent help in 50 per cent. Mestre[338] gave ten *electroshock* treatments to a patient in her menopause; after the third treatment her mental trouble and her asthma disappeared and have not returned for six months. Corbella and his co-workers[128] helped three of four asthmatics by series of ten electroshock treatments.

Physiotherapy for asthma is recommended by Nagera.[355] Sangiovanni[443] obtained very good results in nineteen of twenty patients with bronchial asthma, some with allergic rhinitis and polyposis; symptoms disappeared for one to four months after five intramuscular injections of 10 c.c. *spleen extract*, and spontaneous involution of nasal polyps occurred. In case of recurrence a second or third series of injections led to rapid improvement. Saada and Daire[437] cleared an asthmatic patient for at least seven months by injecting increasing amounts intracutaneously of the patient's own blood drawn during an attack. *Transfusions* of blood probably have no specific effect,[27] but they do aid the strength and resistance in severe asthma, as emphasized by Rackemann and others ("depletion" cases). Transfusions may be dangerous (malaria, syphilis, hepatitis), and through the blood the recipient may temporarily become allergic to a donor's causative allergen, e.g. horse dander or ragweed.

The *surgical* treatment of severe intractable asthma is still favored by some. Carr and Chandler[101] obtained excellent results in all five of their patients; each has gained from ten to 100 lbs., and all have been able to work. The patients whose

operations (dorsal sympathetic ganglionectomy) were performed the longest (ten years) time previously have progressively shown the greatest improvement. Blades[70] obtained good results in four cases by unilateral left-sided parasympathetic denervation and destruction of the pulmonary plexus. Lange[291] says bronchial asthma is in no instance merely a functional disturbance. It is associated with severe pathologic changes in the sympathetic nervous system. Cure of the asthma demands resection of the cervical, thoracic and lumbar ganglia; this procedure cures 30 to 40 per cent. Tourenc[513] did bilateral stellectomies in twenty-two cases of bronchial asthma, with cure in 30 per cent, and improvement in another 25 per cent.

An asthmatic patient of Sterling and Hollander[493] developed faintness, vertigo and numbness after each of two injections of a bacillus pyocyaneus vaccine (bacillus found in sputum and nasal culture). He improved when a vaccine made with staphylococci and streptococci was substituted. Fisher[187] reports good results in six cases of bronchial asthma by increasing intradermal injections of bee and snake venom.

ENDOCRINE INFLUENCE

Hartman[249] has a fine paper on the use of *sex hormones* in allergic disorders. "Allergic phenomena frequently cease or begin at puberty or the climacteric, and during the menacme they may be exacerbated during the menstrual or premenstrual period. At these times the usual satisfactory allergy regimes of elimination and desensitization may be relatively ineffective. . . . In general, allergies appearing at puberty should receive the usual allergy regime plus psychotherapy for the disturbed emotional state until some consistent hormone pattern is established. Menopausal onset or exacerbation is due to uninhibited pituitary overactivity, which may be inhibited by estrogen but also by androgen if bleeding is present. Satisfactory results were obtained in 84 per cent of this group. Menstrual phenomena are usually due to transient estrogen deficiency which can be prevented in 83 per cent of cases by a single large properly timed injection of estrogen just before the expected period. Premenstrual exacerbations or appearances are usually associated with 'premenstrual tension,' the fundamental difficulty being temporary estrogen excess with altered reactivity to same. This can be combated by oral methyl testosterone therapy during the postovulatory and premenstrual phase or by desensitization to estradiol, skin sensitivity to which can be demonstrated. Sixty-seven per cent of the 'premenstrual' group responded satisfactorily to therapy." The vehicle, e.g. peanut or cottonseed oil, may be a factor. Sesame, corn or olive oil allergies are much less common. Vehicle trouble occurs in 4 per cent of cases and should therefore be considered before starting hormone therapy.

PSYCHOSOMATIC ASPECTS IN ASTHMA

There has been considerable interest in this field. Abramson[5] has an excellent historical outline. That anger and hostility influence attacks of asthma goes back at least to the time of Hippocrates, and this concept persisted through the Middle Ages without correlation with known physical causes. The relationship to infection and pathologic residues was pointed out, and the notion of superimposed emotional disturbances was introduced in the eighteenth century. By the beginning of the nineteenth century the notion of repressed emotions entered into discussions as to the cause of asthma. Then came modern immunology and the acceptance of psychoanalytic psychology; and these two fields now must be synthesized by the clinician in theory and in therapy. Abramson[4] also points out that because of the development of physicochemical influences the role of emotional factors in allergy was forced into the background to such an extent that until the past few years none of the standard American books on allergy seriously considered these factors in a systematic way. Thus from 1939 to 1946 "Psychosomatic Medicine" published twenty articles which dealt with emotional problems in allergy. During this same period only one article on this topic was published in the *Journal of Allergy*. In his long article, with thirteen case reports, Abramson points out the importance of emotions, e.g. the man whose asthma was decidedly lessened when he learned to control his temper. The allergists and the psychiatrists must co-operate. [This paper introduced the now famous Round Table at the 1947 annual meeting of the American College of Allergists. It was remarkable to what extent the psychiatrists and the allergists agreed. All members of both groups said that, while psychosomatic influences could not of themselves cause attacks of true bronchial asthma, emotions frequently brought on attacks which simulated asthma and also aggravated asthmatic symptoms in allergic patients. With this concept we heartily agree.] Abramson[3] also discusses the Science of Psychodynamics as applied to allergy.

Mitchell, Curran et al[348] divided 1129 perennial asthmatic patients seen in ten

years into two groups. Group A: typical allergic patterns with positive skin tests and proved extrinsic allergens in 50 per cent; in another 15 per cent in this group bronchial infections complicated the picture; another 12 per cent had miscellaneous anatomic and structural changes. The remaining 344 patients (about 23 per cent) were called Group VM; all diagnostic measures failed to give a clue as to the cause. Of these, 100 were examined as to psychogenic causes and personality problems. The patients were encouraged to talk freely. Maladjustment was diagnosed in 21 per cent (confusion, hostility, fear, guilt feelings, etc.) at the time of their initial interview. In other words, these patients, when allowed to talk, by their own statements showed the picture of personality problems. This was in sharp contrast to the usual clear-cut unemotional statements common to the other diagnostic groups. In this VM group most of the patients were older than in Group A, and females were twice as numerous in the VM group.

Miller and Baruch[345] discuss psychological dynamics in allergic patients as shown in group and individual psychotherapy. Psychogenic factors produce far-reaching biologic changes; in those with allergic constitutions these factors may be expressed as allergic symptoms. Allergic symptoms may represent attempts to gain sympathy, to express hostility, to mask feelings of guilt or anxiety. When emotions were released by psychotherapy, symptoms decreased, and improvement occurred in twenty-one of their twenty-two allergic patients. Baruch and Miller[53] discuss interview group psychotherapy with allergy patients in whom the usual allergy regime had failed. Ten allergic patients were in the group, seven with asthma. The group sessions were held in a warm, cordial and informal manner, with open discussion, and each patient was encouraged to discuss his or her problems. Physical symptoms have disappeared in four of these ten, and have been markedly lessened in three others; the improvement is thought due to the fact that the patients were encouraged to explore and release emotions related to their allergic attacks.

In twenty asthmatic patients Arcaya[39] found that psychiatric factors were important in three, and Cervia[106] reports two more cases. Metzger discusses two cases,[339] and Scolni[449] one. Sternberg[495] states that two patients had the history and findings of seasonal hay fever and asthma but had negative skin tests; both were cured by psychotherapy. Gliebe and Kerr[224] cite two cases of bronchial asthma with positive skin tests, but with unsatisfactory results from allergy regimes. Psychiatric study revealed a difficult home situation in one and an unrequited love affair in the other; solutions of these problems relieved the asthmatic symptoms. A third case was cleared when the allergic patient's mother was removed. It is important to include the psychologic events of the patient's life in the history taking. Swanton[501] has never seen an asthmatic child with a low intelligence quotient. The parents are often overanxious and overprotective, and this may cause frustration in the child with emotional reactions dramatically expressed as asthmatic attacks. Many asthmatics are suggestible; suggestions can precipitate or relieve attacks. In children the psychic treatment is almost solely a matter of educating the parents. "If we do see the child, we do no more than tell him quite confidently, how glad we are that he is now growing up and getting stronger and that we are quite sure his troubles are over and that his attacks of asthma will soon cease. We convey to him the impression that the attacks are quite unimportant and that we are completely unconcerned about them." Weiss[555] says that personality studies suggest a specific relationship between neurotic character structure and allergic disorders. [We do not believe this concept is correct although allergic conditions can and do occur in neurotic individuals as well as in normals.] Other articles on psychosomatic factors come from Walsh and Kierland,[548] Haiman,[230] and Paradela.[372]

GENERAL MEASURES IN ASTHMA

Tetanus toxoid should be routinely used, especially in horse-sensitive patients. This is emphasized by Press,[395] who says that "the conscientious physician, aware of the widespread distribution of tetanus spores, knowing the potentiality of tetanus with trivial injuries and being unable to determine which cases might go on to develop it, would be forced to give tetanus antitoxin for nearly all injuries. In view of the definite effectiveness of tetanus toxoid and its almost complete freedom from adverse reactions, its use seems to be indicated." Press advises simultaneous toxoid when tetanus antitoxin is necessary. An editorial on Tetanus in the United States Army in World War II[169] discusses the exceedingly low number of cases of tetanus in those who received the toxoid; only twelve cases in the entire Army; only six of these had received the full prophylactic doses, including the booster dose when wounded. Peshkin and Rappaport[381] prefer eluted calcium phosphated diphtheria toxoid as this preparation gave fewer local reactions in fifty-five allergic children than alum-precipitated toxoid.

Fuchs[207] studied allergic problems in *elderly patients*. He treated the hay fever of 222 patients as in the young, but in 200 elderly asthmatics he used very little vasoconstrictor drugs because of possible cardiac or cerebral accident; he never gives more than 3 to 5 drops of epinephrine and he does not use epinephrine oil in these patients because it raises blood pressure for a long time. He also avoids morphine, but likes aminophyllin, glucose, oxygen, and ether in oil. He gives digitalis during severe and prolonged attacks to prevent heart failure. He uses nasal sprays and drops very sparingly. He observed benefit in 84 per cent of patients with hay fever, 70 per cent with asthma, and 71 per cent with perennial rhinitis. About 75 per cent of his patients had pulmonary or cardiovascular complications and this fact made surgery dangerous. Injections of house dust and a respiratory vaccine usually gave good results; antihistaminic drugs proved disappointing.

Adequate diets in advanced chronic asthma are advocated by Waldbott, Shea and Harrington.[515] In fifty-six cases who averaged 8.1 Kg. below their estimated weight, high caloric diets were given regardless of any positive skin tests or even clinical sensitivity to certain foods. Fifty of the fifty-six patients were able to tolerate the diet, three developed such severe asthma that the diet was abandoned, and three others stopped the diet after a two-week trial because of increased symptoms. In forty patients the average gain in weight was 1.52 Kg.; in ten the weight was stationary; in the three with severe symptoms the average loss was 0.75 Kg. The effect on the asthma closely paralleled the improvement in nutrition. Of the forty who were improved, twelve remained free from attacks for over three months. The authors believe that deficiencies in essential foods contribute to the persistence of asthma, although psychosomatic factors cannot be excluded. The average caloric intake was 2600, and the diet-weight factor was watched for two weeks, then followed for at least three months. One difficulty is that some patients are afraid to eat certain foods. [We, too, have pushed high caloric diets in this type of patient and have disregarded positive skin tests in most of these cases; but we do not give foods which the patients know cause symptoms, e.g. egg, cottonseed, fish or nuts.] Rackemann[104] outlines the hospital routine care of asthmatic patients. In one ward all the patients did well because the nurse was very much interested, talked to the patients, encouraged them, listened to their problems, and often passed valuable information to the physician. The room was bright and inspiring. In the other ward the nurse was also well trained but she was a poor manager, and the patients with or without asthma consistently fared badly. "The knowledge that someone cares for him as a person in trouble may be as important to the patient as the treatment of his symptoms."

In these days flying is common. Robson[421] believes that most invalids do well in the air. Among the conditions which ordinarily contraindicate flying are hypertension, angina pectoris, recent myocardial infarction, recurrent asthma, emphysema, upper respiratory catarrh and pulmonary tuberculosis. Tillisch and Guilford[512] say persons with asthma should not fly during an acute attack or if they have frequent severe spells; those with mild asthma may safely fly between attacks. Levinton[297] says most asthmatics can do certain exercises, e.g. bicycling, fishing, swimming and rowing.

Status asthmaticus is discussed by several. Bubert and Cook[95] point out that examination may reveal areas of ominous silence where lung tissue has ceased to function because of obstruction by mucus plugs. He advises hospitalization, oxygen, butanefrin 2 mg. intramuscularly for six doses, epinephrine, control of any infection, theoglycinate by aerosol, and aminophyllin intravenously. Feurst[209] tries to remove the cause; his therapy is about the usual, and he is cautious as regards narcotics. He prefers chloral hydrate, paraldehyde or barbiturates though he does use small doses of dilaudid. Michelet[341] reviews the various measures; he never gives epinephrine or other sympathomimetic drugs; he uses oxygen, even subcutaneously; he observed good results from insulin shock therapy, 1 per cent sulfur in oil fixation abscess, or anesthesia. An answer to a query on status asthmaticus[28] ably states that "the seriousness of the condition demands experience and flexibility in the treatment of the various symptoms that may arise. Above all, excessive therapy must be avoided. . . . Neither meperidin (Demerol) nor morphine should be used . . . because of the danger of respiratory depression. . . . Unlike morphine, which acts to produce bronchospasm, meperidin produces bronchodilatation. This, however, is not sufficient to overcome its disadvantages as a respiratory depressant." This latter statement immediately provoked a reply by Barach[129] who agrees with the statement about morphine but says "the effects of ordinary doses of meperidin on the respiration are negligible." He gives 50 to 75 mg. at six to eight hour intervals for four to six days, but large amounts of barbiturates should not be given with Demerol. The danger of addiction should be recognized but not overemphasized. On the same page Rowe gives his therapy for status asthmaticus; food allergy is stressed; "opiates and seda-

tives are contraindicated in all cases." [We never use morphine; we use a little Demerol at times and as little other sedation as possible; we certainly do not agree with Rowe's advice against all sedation as one must give some rest to these sufferers. Since we adopted the continuous method of aminophyllin intravenously we have had much less need for sedation and recovery from the attacks has been accelerated].

Halpin[233] is cautious with sedation and wisely adds Vitamin B and C in many cases; bronchoscopy may be life-saving. Thomas and Thomas[509] rightly stress reassurance; they use Demerol cautiously and bronchoscopy and antibiotics when necessary. (They also agree with Waldhott that to prevent reactions in skin testing one should be cautious when the history indicates extreme sensitivity and should use very dilute extracts for their intradermal tests or even omit testing with highly allergenic extracts). [We strongly urge preliminary scratch tests in such cases—no danger].

Alèmany-Vall[13] discusses treatment of asthmatic crises. Tuberculosis is frequently a factor in his patients in Spain, and in such cases the asthma responds promptly and satisfactorily to tuberculin. He also gives 10 to 20 units of insulin to the many asthmatics who have hyperglycemia; injections of sulfur help, especially if the sedimentation rate is normal. Venesection (200 c.c.), aminophyllin, 25 to 50 per cent glucose intravenously or 5 per cent infusions, helium and oxygen are useful. He likes aerosol with aminophyllin or 10 c.c. of a 5 per cent solution of ammonium chloride. "Bronchoscopy, so favored by American authors, has never solved a problem among us." Vaccines and iodides are favorable in most cases.

Barach's[50] articles on "Physiologic Therapy in Diseases of the Respiratory Tract" emphasize "forms of treatment that were largely outgrowths of studies on the pathologic physiology of respiratory illness. Its basic purpose may be defined as the attempt to correct deviations from the normal functioning of the lungs and bronchi and to eliminate, whenever possible, reversible pathology in these organs." The inhalation of oxygen, carbon dioxide, helium, and the bronchodilator and antibiotic aerosols are discussed. He also stresses types of pressure used: (a) "continuous positive pressure in the treatment of obstructive dyspnea and pulmonary edema; (b) equalizing the pressure on the inner and outer surface of the chest wall to produce arrest of lung movement, providing a new type of local lung rest for the treatment of pulmonary tuberculosis; and (c) intermittent negative pressure applied to the accessory nasal cavities by which air within the sinuses is replaced with a penicillin mist for the treatment of acute and chronic purulent sinusitis." Barach and Garthwaite[48] recommend inhalation of 50 to 70 per cent oxygen with administration of Demerol and iodides as the best treatment for intractable bronchial asthma.

Prevention of asthma is stressed by two laymen, A. S. and R. P. Little.[303] The article is well written though it contains such statements as "Your doctor will probably start with house dust for if this is negative further tests may be unnecessary." Duchaine[100] points out that when respiratory allergy appears in childhood and is inadequately treated, it results in irreversible damage such as chronic bronchitis and emphysema. At this stage symptomatic treatment brings only partial relief to the disabled patient who becomes a charge of his family or his community. The medicosocial measures which might prevent early respiratory allergy are stressed. At the first symptoms, desensitization should be used, especially in children; this should be done in properly equipped establishments. Duchaine describes the working of a future "Health Center for Respiratory Diseases in Children." It should have air-conditioning, antiallergic bedding, wards for aerosol therapy, ultra-violet lights and respiratory gymnastics. House dust, mainly from bedding, and two grasses are the main causes of asthma in children in Belgium. [We applaud Duchaine's vision; such centers should be set up in every large community].

Coca[119] describes "Dust-Seal," the trade name of a product used to immobilize allergenic house dust in floor coverings and other fabrics. The material is an oily emulsion and is sprinkled on rugs; fabrics are soaked in the emulsion. In six patients, three of whom had asthma, this procedure induced marked improvement. [One should add that [illegible] available and this, along with impervious bedding covers, will [illegible] of house dust in dust-sensitive patients. The use of Dust-Seal or similar products will also lessen the amount of dust]. There is an excellent article on the prevention of asthma in industry by Gray and Albert,[227] with case reports on asthma from feathers in a feather-worker, from fur and fur dyes, flour, cadmium fumes (Plater's asthma), and insecticide. They stress removal of all individuals with preasthmatic symptoms from such occupational environments.

There are many other articles on the treatment of asthma, most written in a general way. Among these are papers by Spain.[485,486] Balyeat[67] likes iodized oil intratracheally in the treatment of asthma and/or bronchiectasis; the oil pushes up the infectious

material so that the patients can raise it and this prevents absorption of toxic material. Balyeat also observes good, though temporary, relief by x-ray therapy. Fructier[206] says Antergan (0.6 to 0.8 gm. daily) prevents attacks of asthma; he also injects 5 c.c. 1 per cent novocain intravenously in chronic asthma in exactly seventy-five seconds; he likes insulin shock, aerosol, tuberculin, and gold salts. Koelsche[285] says one-third of all patients with ragweed hay fever ultimately develop asthma unless desensitization is used. Adamson[8] spent several months with Rowe and commends his allergy regime. Agnoli[9] has helped patients by electroshock and lumbar puncture, and by eupaverin and novocain intravenously. Araujo Cintro[35] follows Urbach's method of oral desensitization with foods; he injects for inhalant allergy; he also uses other therapy including 5 per cent peptone, autochemotherapy, injections of histamine (23 per cent clinical "cures" in seventy-two cases), and coramin. Alexander[13] points out that asthma and other allergic conditions which develop after the third decade differ from early allergies. The role of bacterial allergy is still debatable. [We agree with his statement that the scope of allergy requires a broad knowledge of medicine and the future of the study of allergy lies in attracting the interest of men away from the restricted applications of the specialty into the broader fields of medicine. But this statement of Alexander should not let us abandon the cornerstone of successful treatment of allergic patients, i.e., the search for and the removal of the cause wherever possible, and hyposensitization for allergens which cannot be completely avoided]. Smith[477] has an article on "Cures" for asthma and hay fever, written for lay consumption.

Other general articles have been written by Schutzbank,[417] Vilar Bonet,[538] G. T. Brown,[80] Burrage,[98] Cesâri,[107] Feinberg,[182,183] Zussman,[560] Sanchez-Cuenca,[441] Oner,[370] Oliveira Lima,[365] T. Nelson,[500] MacInnis,[326] Frouchtman,[201,203] Harris,[245] and Crandall.[135] A panel discussion on the treatment of asthma was participated in by Piness, Tuft, Eyerman, Cooke and Black;[367] psychogenic factors are probably important in 50 per cent of the adults, less in younger patients; dry hot climates are best although some patients do better in dry, cold locations; penicillin rarely gives permanent relief and is not indicated unless infection is associated. Demerol, opium, and especially morphine are to be avoided.

BIBLIOGRAPHY

1. Abramson, A. A.: Comment. Quart. Rev. All., 2:260, 1948.
2. Abramson, H. A.: Penicillin aerosols of high concentration. Science, 106:316, 1947.
3. Abramson, H. A.: Present status of allergy. Nervous Child, 7:86, 1948.
4. Abramson, H. A.: Psychodynamics and the allergic patient. Ann. Allergy, 6:219, 1948.
5. Abramson, H. A.: Psychosomatic aspects of hay fever and asthma prior to 1900. Ann. Allergy, 6:110, 1948.
6. Abramson, H. A.: Vitamin C aerosol for inhalation therapy of the lung. Fed. Proc., 6:233, 1947.
7. Adams, W. E.: Congenital lung cysts. J. Internat. Coll. Surgeons, 10:558, 1947.
8. Adamson, C. A.: Rowe's methods in treating allergic diseases. Manitoba M. Rev., 27:301, 1947.
9. Agnoli, R.: Antiallergic measures. Gaz. Sanitaria, 18:11, 1947.
10. Allan, W. B.: Bronchiectasis. Modern treatment. South. M. J., 41:1049, 1948.
11. Alemany-Vall, R.: Resumen of few cases of asthma and rhinitis caused by flour. Medicamenta, 145:10, 1948.
12. Alemany-Vall, R.: Resumen of rhinitis and asthma caused by pollen. Anales de Medicina, Barcelona, 34:1, 1947.
13. Alemany-Vall, R.: Treatment of the asthmatic crisis. Med. Clinica, 10:353, 1948.
14. Alemany-Vall, R.: Tuberculosis and asthma, 133 pp., Estudios Monograficos de Investigacion Medica, Barcelona, 1946; Tuberculin sensitivity and clinical forms of tuberculous asthma. Med. Clinica, 7:168, 1946.
15. Alexander, H. L.: Allergy from perspective of general medical practice, J.A.M.A., 136:762, 1948.
16. Alexander, H. L.: Synopsis of allergy. J.A.M.A., 136, Feb. 28, 1948.
17. Alexander, H. F., Wilson, K. S., et al.: Bronchial asthma. J. Missouri M. A., 44:664, 1947.
18. Alford, R. L.: Allergy in Japan. J. Allergy, 19:240, 1948.
19. Alonso, L., and Adams, M.: Mode of action of antihistaminic drugs. Federal Proc., Balt., 7:1, 1948.
20. Aluminum pneumoconiosis. Brit. Med. J., 4549: 496, 1948.
21. Alvarinas, C., Solari, M. A., and Rivero, E.: Intestinal parasites and allergic syndromes. Rev. Assoc. Argent., 5:37, 1947.
22. Andre, M. J.: Fatal attack of asthma. Acta Clin. belg., 2:1 (Jan.-Feb.), 1947.
23. Anderson, E. W.: Solitary lung cysts. Symptomatology, diagnosis and treatment. Nord. Med., 35:1703, 1947.
24. Answer to Query. J.A.M.A., 137:1640, 1948.
25. Answer to Query. J.A.M.A., 136:289, 1948.
26. Answer to Query. J.A.M.A., March 20, 1948.
27. Answer to Query Transfusion Asthma. J.A.M.A., 138:168, 1948.
28. Answer to Query. J.A.M.A., 135:260, 1947.
29. Answer to Query. J.A.M.A., 136:443, 1948.
30. Answer to Query. J.A.M.A., Feb. 21, 1948.
31. Answer to Query. J.A.M.A., Aug. 21, 1948.
32. Answer to Query. J.A.M.A., 137:758, 1948.

33. Answer to Query. J.A.M.A., 134, Aug. 30, 1947.
34. Antihistaminic drugs. Brit. M. J., 4559:999, 1948.
35. Araujo Cintra: Treatment of asthma. Med. cir. farm., Rio, 13:319, 1947.
36. Arbesman, C. E.: Comparatus studies of several antihistamine drugs. J. Allergy, 19:178, 1948.
37. Arbesman, C. E.: Pharmacology of Pyribenzamine and Benadryl. New York State J. Med., 47:1775, 1947.
38. Arbesman, C. E., Cohen, V. L., and Osgood, H.: Pyribenzamine versus specific hyposensitization. J. Allergy, 18:311, 1947.
39. Arcaya, A.: Psychogenic factors in bronchial asthma. Rev. Méd. de Chile, 75:454, 1947.
40. Archibald, H. C.: Allergy in childhood. The Long Range View. Arch. Pediat., 64:192, 1947.
41. Ayerbe, S. A.: Bronchiectasis in infancy. Rev. españ. de tubere., 16:11, 1947.
42. Baaghe, K. H.: Allergy and allergic disposition. Nord.-med., 34:1413, 1947.
43. Baaghe, K. H.: Pre-Asthmatic stage of asthma. Acta Allerg., K.B.H., 1:197, 1948.
44. Badger, T. L.: Bronchiectasis: Treatment and prevention. New England J. Med., 237:937, 1947.
45. Baker, J.: Allergy in children as related to altitude. Ann. Allergy, 6:33, 1948.
46. Ballantine, A. J.: Treatment of asthma. South African M.J., 21:733, 1947.
47. Balyeat, R. M.: Relative value of some non-specific therapeutic measures in treatment of asthma. Balycat Hay Fever and Asthma Clin. Proc., 17::2, 1947.
48. Barach, A. L., and Garthwaite, B.: Physiologic and antibiotic therapy of intractable bronchial asthma. Ann. Allergy, 5:297, 1947.
49. Barach, A. L.: Physiologic therapy in respiratory diseases. J.A.M.A., 138:391, 1948.
50. Barach, A. L.: Physiologic therapy in diseases of respiratory system. J. Mt. Sinai Hosp., 14:857, 1947; Physiologic therapy of intractable bronchial asthma and status asthma. Am. Practitioner, 2:703, 1948; Physiologic and antibiotic therapy of bronchial asthma. Connecticutt M.J., 11:819, 1947.
51. Barnett, R. N.: Reactions to a bismuth compound (suppositories). J.A.M.A., 135:28, 1947.
52. Bartlett, C. L.: Ethylene disulfonate in allergy. M. Rec. N. Y., 160:467, 1947.
53. Baruch, D. W., and Miller, H.: Interview Group Psychotherapy With Allergy Patients. Practice of Group Therapy, 156.
54. Baumann, F., Crump, J., Arthurs, A. C., Saeger, L. D. and Miller, R. E.: Penicillin therapy in bacterial asthma. J.A.H.H. Women's A., 2:442, 1947.
55. Becker, E. L., and Rappaport, B. Z.: Quantitative studies in skin testing II. J. Allergy, 19:317, 1948.
56. Becker, G.: Atypical asthma. Acta Allerg. K.B.H., 1:211, 1948.
57. Benson, R. L., and Perlman, F.: Clinical effects of epinephrine by inhalation. J. Allergy, 19:129, 1948.
58. Bentolila, L.: Allergy in pediatrics. Rev. Soc. pediat. d. litoral, 1:255, 1946: Pediat. Américas, 5:491, 1947.
59. Berman, E. I.: Transitory eosinophilic infiltrations of lungs in children. Pediatriya, 1:33, 1947.
60. Bernstein, T. B., Rose, J. M., and Feinberg, S. M.: New antihistaminic drugs. Illinois M.J., 92:90, 1947.
61. Bernton, H. S.: Paraxysmal dyspnea, case report. Ann. Allergy, 6:317, 1948.
62. Berre: Aerosols. Rev. Méd. Hav., 2:259, 1947.
63. Berry, J. W.: Aluminum therapy in silicosis. Am. Rev. Tuberc., 57:557, 1948.
64. Bertrand-Fontaine Mme., Goutner, and Noufellard, H.: Multinodular form of Löffler's syndrome due to ascaris. Bull. et mém. Soc. méd. de hôp. de Paris, 63:700, 1947.
65. Biering, A.: Atelectatic bronchiectasis. Two Cases. Nord. med., 35:1884, 1947.
66. Bisby, G. R., et al: The fungi of Manitoba and Saskatchewan. National Research Council of Canada, 189 pp.
67. Bisher, M. S.: Pulmonary hydatid cyst with asthma. Case report. J. Roy. Egypt. M.A., 30:341, 1947.
68. Bizzozero, R. C.: Cardiac insufficiency. Día. med., 19:1176, 1947.
69. Black, J. H.: Influence of respiratory allergy upon life and health of the individual. J. Insur. M., 3:34, 1948.
70. Blades, B.: Surgical treatment of intractable asthma. Post-Grad. Medicine, 4:1, 1948.
71. Blaisdell, I. H.: Bronchography. Laryngoscope, 58:288, 1948.
72. Blamoutier, P.: Asthma from house dust. La Sem. des hôp. de Paris, 24:664, 1948.
73. Blamoutier, P.: Unusual case of serum allergy by inhalation. La Sem. des hôp. de Paris, 24:659,1948.
74. Blumenthal, L. S., and Rosenberg, M. H.: Benadryl hydrochloride. J.A.M.A., 135:20, 1947.
75. Bodman, J., and Felix, E.: Chronic bronchial asthma and other allergic states treated by ethylene disulphonate. Digest. of Treatment, J. B. Lippincott Co., 11:496, 1948.
76. Bohrod, M. G.: Classification of the histologic reactions in allergic diseases. Am. J. Med., 3:511, 1947.
77. Bonnier, M.: Forty-five cases peanuts removed from lower respiratory passages. Ann. Otol. Rhin. & Laryng., 56:784, 1947.
78. Bowen, R.: Asthmatic children. Journal Lancet, 58:169, 1948.
79. Bowman, J. R.: Sinusitis as cause of chronic cough in children. J. Tennessee M.A., 38:215, 1945.
80. Branderberg, O., and Wilander, O.: Desensitization in allergic disease in children. Ann. paediat., 166:250, 1946.
81. Bresnick, E., Woodard, W. K., and Sageman, C. B.: Fatal reactions to intravenous administration of aminophyllin. Report of Three Cases. J.A.M.A., 136:397, 1947.
82. Brewster, J. M.: Benadryl as a therapeutic agent in treatment of common cold. U. S. Naval M. Bull., 47:810, 1947.
83. Bronfenbrenner, J.: Hypersensitivity and immunity in the light of the "Unitarian" Hypothesis. J. Allergy, 19:71, 1948.
84. Brown, A.: Asthma in child precipitated by carbohydrate dyspepsia. Glasgow M.J., 29:33, 1948.
85. Brown, E. A.: A clinical evaluation of a new antihistamine agent "Trimeton". Ann. Allergy, 6:393, 1948.
86. Brown, E. A.: Progress in allergy. Respiration. A review of recent literature. Ann. Allergy, 5:381, 1947.
87. Brown, E. A.: Use of respiratory enzyme, Cytochrome C., in dyspnea. Ann. Allergy, 5:571, 1947.
88. Brown, E. A., Weiss, L. R., and Maher, J. R.: The clinical evaluation of Decapryn. Ann. Allergy, 6:1, 1948.

89. Brown, E. B., and Brown, F. W.: New antihistaminic combination in the treatment of allergic disorders. New York State J. Med., 48:1465, 1948.
90. Brown, G. T.: General review of allergy. M. Ann. District of Columbia, 16:675, 1947.
91. Broyles, L. N.: Bronchospropie experiences with tumors of lower respiratory tract. Ann. Otol. Rhin. & Laryng., 57:129, 1948.
92. Bruce Pearson, R. S.: Asthma. Brit. M.J., Jan. 3, 1948.
93. Bryson, V., and Grace, E. J.: Aerosol therapy of respiratory diseases. New England J. Med., 237:683, 1947.
94. Buhert, H. M., and Cook, S.: Combined theoglycinate and penicillin aerosol in the treatment of severe asthma. Bull. U. of Maryland, 32:175, 1948.
95. Buhert, H. M., and Cook, S.: Status asthmaticus. South. M.J., 41:146, 1948.
96. Buffman, W. P.: The characteristics of asthma in infancy. Rhode Island M.J., 30:859, 1947.
97. Burnet, F. M.: Basis of allergic diseases. M.J. Australia, 1:29, 1948.
98. Burrage, W. S.: Allergy. New England J.M., 238:770, 1948.
99. Burrage, W. S.: Recent therapeutic trends in allergy. New England J.M., 238:181, 1948.
100. Cameron, D. E.: Increased reactivity caused by adrenaline. Am. J.M. Sc., 213:351, 1947.
101. Carr, D. and Chandler, H.: Dorsal sympathetic ganglionectomy for asthma. J. of Thoracic Surg., 17:1, 1948.
102. Carr, D., Denman, W. E., and Skinner, E. F.: Noxious gases and bronchiectasis. Dis. of Chest, 13:596, 1947.
104. Castillo, J. C., and DeBeer, E. J.: The tracheal chain. Antispasmodics and Bronchodilator Drugs. J. Pharmacol. & Exper. Therap., 90:104, 1947.
105. Cavallero, C.: Allergic diseases due to fungi. Mycopathologia, 4:1, 1947.
106. Cervia, T.: Psychogenic factors in bronchial asthma. Rev. clin. españ., 21:498, 1946.
107. Cesari, G.: Classification of asthma. Rassegna intermar. di clin. e terap., 26:385, 1946.
108. Cetrángolo, R.: Complications and sequels of asthma. Rev. de tubere. d. Uruguay, 14:117, 1946.
109. Chapman, D. W.: Cardiac condition simulating pulmonary lesions. M. Rec. & Ann., 41:233, 1947.
110. Charlier, R.: Therapeutical studies in bronchial asthma with aerosols of aleudrin. M. Times, 75:277, 1947.
111. Charlier, R.: Treatment of functional dyspnea with medicated aerosols. Acta clin. belg., 2:313, 1947.
112. Christensen, J. A. and Seidel, R. E.: Hypoglycemia in bronchial asthma. Hahneman Monthly, 82:11, 1947.
113. Christensen, O., Sanne, C.: Relations between skin reactions and provocatory inhalation tests in asthmatic patients. Acta med. Scandinav., 131:555, 1948.
114. Cintra, Araujo: Aerosol penicillin in infections of the respiratory tract. Hospital, Rio de Janeiro, 33:855, 1948.
115. Clark, H., and Rosenberg, B.: Löffler's syndrome associated with ascaris lumbricoides. Clin. Proc. Child. Hosp. Washington, D. C., 3:59, 1947.
116. Claussen, O.: Bronchial asthma in Norway. Statistics on occurrence and significance. Nord. med., 37:525, 1948.
117. Clerf, L. H.: Progress in bronchology. J.A.M.A., 136:733, 1948.
118. Clusellas, F. J.: Meteorology and asthmatic crisis. Semana Méd., 1:340, 1948.
119. Coca, A. F.: Dust Seal. Its use in avoidance of house dust by dust-sensitive patients. Ann. Allergy, 6:506, 1948.
120. Cohen, A. A.: Bronchial asthma in pulmonary tuberculosis. Am. Rev. Tubere., 56:287, 1947.
121. Cohen, E. B., Davis, H. P., and Mowry, W. A.: Thephorin in allergy; a study of 292 cases. Am. J. Med., 5:44, 1948.
122. Cohen, E. H., and Van Bergen, F.: Isuprel, a new bronchodilating agent. Bull. Univ. Minn. Hosp., 19:424, 1948.
123. Cohn, M. B., and Abram, L. E.: Growth pattern of allergic children. Acta Allerg. K.B.H., 1:225, 1948.
124. Conn, S. and Wolf, H. L.: Studies of the autonomic nervous system in "atopic" individuals. I. Palmar Sweating in Allergic Patients: A cholinergic phenomenon. J. Allergy, 18:391, 1947.
125. Colldahl, T.: Pathophysiological and clinical aspects of crises of asthma bronchiale. Acta Med. Scandinav. 128:551, Fasc. 6, 129: 19, Fasc. 1, 1947.
126. Cooke, R. A.: The immunology of allergic disease. Am. J.M., 3:523, 1947.
127. Cor Pulmonale: Current comment. J.A.M.A., 136:44, 1948.
128. Corbella, T., Piredda, F. and Gemignani, V.: Electroshock in asthma. Minerva Med. Tor., 39:52, 1948.
129. Correspondence, J.A.M.A., 136: Feb. 14, 1948.
130. Correspondence, J.A.M.A., Feb. 28, 1948.
131. Correspondence, J.A.M.A., 137, 211, 1948.
132. Cortez, J., Brunner, M., and Altman, L.: Skin tests in dogs with common allergens. J. Allergy, 18:305, 1947.
133. Council Pharmacy and Chemistry. J.A.M.A., 134:955, 1947.
134. Coutinho, A.: Eosinophilia tropical, Hospital, Rio de Janeiro, 33:77, 1948.
135. Crandall, F. G.: Allergy in general practice. Ann. West. Med. & Surg., 1:395, 1947.
136. Criep, L. H.: Histamine antagonists in role of allergy. Journal Lancet, 48:55, 1948.
137. Criep, L. H., and Aaron, T. H.: Neobetramine: an experimental and clinical evaluation in allergic states. J. Allergy, 19:215, 1948.
138. Criep, L. H., and Aaron, T. H.: Thephorin: an experimental and clinical evaluation in allergic states. J. Allergy, 19:304, 1948.
139. Crystal, D. K., Edmonds, H. W., and Betzold, P. F.: Symmetrical double aortic arch. Case report. West. J. Surg., 55:389, 1947.
140. Curry, J. J.: Clinical use of histamine and histaminase, an evaluation. Med. Clinics N. Amer., 1261, Sept., 1947.
141. Curry, J. J.: Comparative action of methacolin and histamine on respiratory tract in bronchial asthma. J. Clin. Investigation, 26:430, 1947.
142. Curry, J. J., and Lowell, F. C.: Vital capacity in asthmatic subjects receiving histamine and acetyl-beta-methyl choline. J. Allergy, 19:9, 1948.
143. Dallas, H. F.: Löffler's syndrome. New York State J. Med., 48:1949, 1948.
144. Danielopolu, D., and Rosenzweig, S.: Traitment de l'asthme, de la maladie etc. Bull. Acad. Nat. Med., 132:7, 1948.
145. D'Arcangelo, D.: Insulin shock therapy in bronchial asthma. Policlinico, 54:920, 1947.
146. Darrough, L. E.: Nasal allergy associated with sinus disease. Texas St. J. Med., 43:285, 1947.

200. Froman, A. L.: Complications of arrested pulmonary tuberculosis. Illinois M.J., 306: (June), 1948.
201. Frouchtman, R.: Allergic paroxysms bronchal asthma. Medicina, Mexico, 27:306, 1947.
202. Frouchtman, R.: Erythrosedimentation rate in allergic diseases, Barcelona, Spain. Medicina Clínica, 8:180, 1947.
203. Frouchtman, R.: Importance of interrogation in allergic disease. Medicina, Mexico, 27:357, 1947.
204. Frouchtman, R., Foz-Tena, A., and Jou, M. M.: Respiratory allergies in Barcelona. Medicina Clinica, 10:171, 1948.
205. Frouchtman, R., and Oriol Anguera, A.: Infectious asthma with hypersensitivity to sulfanilamido-thiazole. Medicina Clínica, 10:48, 1948.
206. Fruchter, M. L.: Treatment of bronchial asthma. Monde Méd., Paris, 57:991, 1947.
207. Fuchs, A. M.: Allergic problems in elderly persons. Geriatrics, 2:235, 1947.
208. Fuchs, A. M., Schulman, P. M., and McGavack, T. H.: Evaluation of Benadryl in bronchial asthma. Am. J.M., 3:309, 1947.
209. Feurst, S. I.: Symptomatic treatment of severe bronchial asthma. Mississippi Doctor, 25:364, 1948.
210. Furstenberg, F. F.: Jewish health migration. Jewish Social Serv. Quart., 24: Sept., 1947.
211. Gaddum, J. H.: Histamine. Brit. M.J., 1:867, 1948.
212. Galup, J.: Fatal evolution of pulmonary emphysema with chronic bronchitis and asthma. Sem. d. hôp. Paris, 23:2003, 1947.
213. Gann, E. L.: Bronchography in bronchiectasis in children. Ann. Otol., Rhin. & Laryng., 17:153, 1948.
214. Garthwaite, B., and Barach, A. L.: Penicillin aerosol therapy in bronchiectasis, lung abscess and chronic bronchitis. Am. J.M., 3:261, 1947.
215. Gay, L. N., and Marriott, H. J. L.: The treatment of infective asthma with penicillin in beeswax and oil. Trans. & Stud. Coll. Physicians, Philadelphia, 15:91, 1947.
216. Gay, L. N.: Pathology of asthma. Clinics, 5:347, 1946.
217. Gelfand, H. H.: Role of thephorin in allergic disorders. New York St. J.M., 48:1947, 1948.
218. Gerstl, B., Tager, M., and Marinaro, N. A.: Pathogenicity of Bagasse disease. Arch. Path., 44:343, 1947.
219. Gilman, A.: Pharmacology of drugs used in allergic conditions. J. Allergy, 19:281, 1948.
220. Ginsburg, M.: Spontaneous fracture of the first rib as a complication of status asthmaticus. Ann. Allergy, 5:489, 1947.
221. Giodano, A. F.: The association of histamine-acetylcholin-heparin in treatment of allergy. Dia. Méd., 19:848, 1947.
222. Giovannoli, F.: Desensitizing action of histamine in bronchial asthma and asthmatic bronchitis. Minerva Med., (Torino), 39:50, 1948.
223. Glaser, J.: Pediatric allergy. A critical review of recent literature. Ann. Allergy, 6:178, 1948.
224. Gliehe, P. A., and Kerr, W. J.: Recognition of emotional factors in allergic manifestations. Am. J.M., 3:607, 1947.
225. Goldman, H. I.: Clinical report on intravenous Benadryl. Rocky Mountain M.J., (Dec.), 1947.
226. Goodman, M. J.: Periarteritis nodosa with recovery. Ann. Int. Med., 28:181, 1948.
227. Gray, I., and Albert, M. M.: Asthma, prevention in industry. Indust. Med., Dec., 1943.
228. Gray, J. S., and Green, E. L.: Voluntary ventilation capacity. Federation Proc., 5:35, 1946.
229. Hagens, E. W., Karp, M., and Farmer, C. J.: Penicillin and streptomycin aerosol in treatment of pulmonary disease. Arch. Otolaryng., 47:138, 1948.
230. Haiman, J. A.: Psychosomatic approach to treatment of allergy, bronchial asthma and systemic disorders. Med. Rec., Kutztown, 161:467, 1948.
231. Halpern, B. N.: Experimental research on a new series of chemical substances with powerful antibistaminic activity: The theodiphenylamine derivatives. J. Allergy, 18:263, 1947.
232. Halpern, B., Hamburger, I., and Cruchano, S.: Recent researches on synthetic antihistamines. Letter from Paris. J.A.M.A., Feb. 20, 1948, p. 841.
233. Halpin, L. J.: Emergency measures in bronchial asthma. J. Iowa M. Soc., 37:454, 1947.
234. Ham, J. C., and Zimdahl, W. T.: Löffler's syndrome. Ann. Int. Med., 29:488, 1948.
235. Hamburger, J.: Notes on the treatment of bronchial asthma. Praxis, (Bern), 37:397, 1948.
236. Hamburger, J.: Subclinical permanent dyspnea in asthmatics. La Semaines des Hôp. de Paris, 24:80, 2257, 1948.
237. Hamburger, J.: Recent progress in treatment of asthma. La Semaines des Hôp. de Paris, 23:2025, 1947.
238. Hamburger, J., Milliez, P., and Halpern, B.: Role of sympathomimetic drugs in asthma. Bull. Soc. Méd. Hôp. Paris, 63:432, 1947.
239. Hamburger, J., Milliez, P., and Halpern, B.: Status asthmaticus. Ann. de Méd., 49:186, 1948.
240. Hamburger, J., Halpern, B., and DeGeorges: Studies on bronchial asthma I: Test of the Average Expiratory Rate. Ann. de Méd., 49:173, 1948.
241. Hansel, F. K.: Nethaphyl in treatment of nasal allergy and bronchial asthma. Ann. Allergy, 5:397, 1947.
242. Hanzlik, P. J.: Recovery from a surely fatal dose of epinephrine. California Med., 66:104, 1947.
243. Hardy, H. L.: Delayed pneumonitis caused by beryllium. Am. Rev. Tuberc., 57:547, 1948.
244. Harley, D.: New antihistaminic drugs. Report on Benadryl. Practitioner, 158:482, 1947.
245. Harris, M. C.: Present day treatment in asthma. California Med., 66:354, 1947.
246. Harsh, G. F.: A comparative study of commercial nebulizers. Ann. Allergy, 6:534, 1948.
247. Hartman, M. M.: Antiasthmatic effects of compound 887. Ann. Allergy, 5:536, 1947.
248. Hartman, M. M.: The newer drugs for allergic disorders. California Med., 66:242, 1947.
249. Hartman, M. M.: Use of sex hormones in allergic disorders. Ann Allergy, 5:467, 1947.
250. Henderson, A. T., and Pierce, C. B.: Löffler's syndrome. Am. J. Roentgenol., 58:391, 1947.
251. Henderson, A. T., and Rose, B.: Pyribenzamine in treatment of allergy. Canad. M.A.J., 57:136, 1947.
252. Henrici's molds, yeasts and actinomycetes: by Skinner, C. E., Emmons, C. W., and Tsuchiya, H. M., J.A.M.A., Aug. 16, 1947.
253. Henriksen, E.: Follow up examination concerning specific desensitization of asthma patients. Acta Allerg., K.B.H., 1:204, 1948.
254. Herxheimer, H.: Aleudrin and anthisan in bronchial spasm. Lancet, London, 1:926, 1948.
255. Herxheimer, H.: Antihistamine drugs. Brit. M.J., 1:999, 1948.
256. Herxheimer, H.: Symptomatic treatment of bronchial asthma. Practitioner, 159:399, 1947.

314. Lowance, M. I., Jones, E. C., Mathews, W. B., and Duncan, E. M.: Two cases of bullous emphysema. Differential diagnosis from bronchial asthma. South. Med. & Surg., 109:253, 1947.
315. Loveless, M. H.: Therapeutic and side effects of Pyribenzamine and Benadryl. Am. J. Med., 3:296, 1947.
316. Loveless, M. H., and Brown, H.: Comparison between clinical effects of Pyribenzamine and Benadryl. New England J. Med., 237:501, 1947.
317. Lowell, F. C., and Schiller, I. W.: Changes in vital capacity to inhaled aerosolized allergenic extracts in asthmatic subjects. J. Allergy, 19:100, 1948.
318. Lowel, F. C., and Schiller, I. W.: The induction of asthma like attacks in subjects with "Idiopathic" Asthma. J. Allergy, 19:172, 1948.
319. McGavack, T. H., Elias, H., and Boyd, L. J.: Some pharmacological and clinical experiences with Benadryl. Am. J. M. Sc., 213:418, 1947.
320. McGavack, T. H., Schulman, P. M., and Boyd, L. J.: A clinical investigation of Linadryl. J. Allergy, 19:141, 1948.
321. McGee, W. A.: Early recognition of allergic tendencies in infancy. South. M. J., 40:515, 1947.
322. McGee, W. A.: The important role of allergy in pediatrics. South. M. J., 41:139, 1948.
323. McQuiddy, E. L.: Personal communication to Wm. S. Merrell Co.
324. McRae, D. F.: Congenital cystic disease of lung. Canad. M.A.J., 57:545, 1947.
325. Mack, Grossman, and Katz.: Am. J. Physiol., 150:654, 1947.
326. MacInnis, K. B.: What's new in allergy? J. South Carolina M. A., 43:264, 1947.
327. MacInnis, K. B.: X-ray therapy as adjuvant in bronchial asthma. South. Med. & Surg., 109:305, 1947.
329. Madison, F. W.: Diagnostic aids in periarteritis nodosa. Am. Practitioner, 2:791, 1948.
330. Mallet, J. R.: Aerosols and Asthma. J. de med. de Bordeaux, 128:346, 1948.
331. Mallory, T. B.: Pathogenesis of bronchiectasis. New England J. Med., 237:795, 1947.
332. Markow, H., Bloom, S. and Leibowitz, H.: An evaluation of hydryllin in symptomatic Treatment of Allergy, New York State J. Med., 48:2390, 1948.
333. Marsh, D. F.: Antihistaminic agents. West Virginia M. J., 44:265, 1948.
334. Martins, J. K.: Allergy, use of thenylene HCl in treatment of. Indust. Med., 47:133, 1948.
335. Mascheroni, H., Bensi, C., Ituohe, R. R., and Coste, R. H.: Subcutaneous emphysema in bronchial asthma. Rev. Assoc. Med., B. Air. Argentina, 61:226, 1947.
336. Maunsell, K., Whetnall, E., and Rimington, C.: The allergens of house dust: diagnosis and desensitization of dust-sensitive patients with "crude dust antigen." Brit. J. Exper. Path., 28:331, 1947.
337. Melich, R., et al: Intrinsic asthma. J. Florida M. A., 34: (Aug.) 1947.
338. Mestre Mestre, B.: Electroshock therapy in a case of asthma. Med. Clin., Barcelona, 9:30, 1947.
339. Metzger, F. C.: Emotions in the allergic individuals. Am. J. Psychiat., 103:697, 1947.
340. Miale, N. B., Doege, K. H., and Piehl, M.: Panarteritis in allergic persons. Arch. Int. Med., 80:791, 1947.
341. Michelet, L.: Modern treatment of status asthmaticus. La Clinique, 43:412, 1948.
342. Mickle, W. A., Jr.: Studies on causation of unusual pulmonary disease at Camp Gruber, Oklahoma. Arch. Int. Med., 80:203,1947.
343. Milhaud, Delore, Valin, and Mme. Yver: Asthmatics at the Lyon Selection Center for the Thermal Therapeutic Resorts. Gaz. Méd. France, 55:69, 1948.
344. Miller, H.: Modern concepts of the immunologic basis of clinical allergy. Northwest Med., 47:22, 1948.
345. Miller, H., and Baruch, D. W.: Psychological dynamics in allergic patients as shown in group and individual psychotherapy. J. Consult. Psychol., 12:111, 1948.
346. Miller, M.: Modern concepts of pathologic physiology of bronchial asthma. Northwest Med., 47:432, 1948.
347. Miller, M. W.: Penicillin in intractable asthma. J. Allergy, 18:109, 1947.
348. Mitchell, J. H., Curran, C. A., Mitchell, W. F., Sivon, I., and Myers, R.: Personality factors in "allergic" disorders. J. Allergy, 18:337, 1947.
349. Moody, A. M.: Asphyxial death due to pulmonary cryptococcosis. Case report. California Med., 67:105, 1947.
350. Morrow, M. D.: Mold fungi in etiology of respiratory allergic diseases. VII. Further survey studies. Ann. Allergy, 5:442, 1947.
351. Myers, W. A.: Allergic rhinitis and asthma in infants and children. Proc. Staff Meet., Clin. Honolulu, 13:103, 1947.
352. Myerson, R. M.: Spontaneous pneumothorax. New England J. Med., 238:461, 1948.
353. Naclerio, E. A., and Langer, L.: Adenoma of bronchus. Am. J. Surg., 75:532, 1948.
354. Naef, A. P.: Bronchiectasis, a surgical disorder. Praxis, Bern, 37:639, 1948.
355. Nagera, J. M.: Kinesiterapia del asma. Semana méd., 54:65, 1947.
356. Nance, F. D.: Asthma in newborn or "Doctor . . . is it thymus?" Hawaii M. J., 6:400, 1947.
357. News Item. J.A.M.A., 135:1252, 1947.
358. Newton, A., Sherago, M., and Weaver, R. H.: Mold distribution in air and dust in Kentucky. Ann. Allergy, 6:260, 1948.
359. Nickerson, W. J.: Biology of pathogenic fungi. Chronica Botanica. Waltham: Mass. Pp. 236.
360. Nicod, J. L.: Present-day problems in silicosis. Bull. Acad. de Méd., Paris, 130:685, 1946.
362. Norén, B., and Feinberg, R. H.: Histamine antagonists, XI. J. Allergy, 19:90, 1948.
363. O'Byrne, G. T.: Löffler's syndrome. Case report in infant. Texas State J. Med., 43:446, 1947.
364. O'Keefe, E. O.: Some aspects of pediatric allergy. J. Maine M. A., 35:3, 1948.
365. Oliveira Lima, A.: Pathology, diagnosis and treatment of asthma. Semana méd., 2:989 and 1029, 1947.
366. Olsen, A. M.: Nebulization therapy in bronchiectasis. J.A.M.A., 134:947, 1947.
367. Ordman, D.: Buckwheat allergy. South African M. J., p. 737. Oct. 11, 1947.
368. Ordman, D.: Pollinosis in South Africa. South African M. J. 21:38, 1947.
369. Ornstein, G. G.: Emphysema of the lungs. Quart. Bull. Sea View Hosp., 9:89, 1948.
370. Over, R. A.: Advances in allergy. San Diego Co. M. Bull., Sept. 1947.
371. Overholt, R. H., Betts, R. H., and Woods, F. M.: Multiple segmental resection in the treatment of bronchiectasis. Dis. of Chest, 13:583, 1947.
372. Paradela, A.: Psychic allergy. Med. Clin. Barcelona, 8:198, 1947.

431. Rowe, A. H., Jr., and Rowe, A. H.: Local cutaneous allergy (Arthus phenomenon) from epinephrine. J. Allergy., 19:62, 1948.
432. Rubin, H., and Glass, G. D.: Pneumoperitoneum in treatment of bronchial asthma. Canad. M. A. J., 59:162, 1948.
433. Rucks, W. L.: The allergic child. Ann. Allergy. 6:52, 1948.
434. Rudner, C.: New drug for control of cough in chronic pulmonary disease. South. M. J., 40:521, 1947.
435. Ruiz-Moreno, G., and Bachman, A. E.: Contribution to the treatment of asthma with nebulizations of antibiotic substances. Allergia, Buenos Aires, 1:9, 1947.
436. Ruskin, S. L.: Sodium ascorbate in treatment of allergic disturbances. Am. J. Digest. Dis., 14:302, 1947.
437. Saada and Daire: Asthma cured by progressive intradermal autoserotherapy. Algérie Méd., p. 495, 1947.
438. Salén, E. B.: Asthma in children, its diagnosis, treatment and prognosis. Svenska Läktidning, 43:18, 1946.
439. Salén, E. B., and Atner, B.: Some views on the aspirin-hypersensitive allergy group. Acta Allergologica, 1:47, 1948.
440. Samter, M.: Charcot-Leyden crystals. A study of the conditions necessary for their formation. J. Allergy, 18:221, 1947.
441. Sanchez-Cuenca, R.: Maticcs Clinicos del Asma Bronquial. Bol. del Instituto de Patologia Méd., 1:165, 1947.
442. Sander, O. A.: Benign pneumoconiosis due to metal fumes and dusts. Am. J. Roent. and Rad. Therapy, 58:277, 1947.
443. Sangiovanni, V.: Spleen extract in therapy of bronchial asthma. Pract. Oto., Rhin. Laryng., 9:79, 1947.
444. Schiller, I. W., and Lowell, F. C.: Effect of drugs in modifying response of asthmatic subjects to inhalation of pollen extracts. Ann. Allergy, 5:564, 1947.
445. Schmidt, H. W.: A method of obtaining bilateral bronchograms. Proc. Staff Mayo Clin., 71, Feb. 4, 1948.
446. Schutzbank, F. H.: Climatotherapy in treatment of allergic diseases. J. Allergy, 19:244, 1948.
447. [illegible]: Clinical aspects of bronchial asthma. Arizona Med., January, 1948.
448. [illegible] ergy. J. Allergy, 18:341, 1947.
449. [illegible] of asthmatic boy. Rev. Psicoanál., 4:664, 1947.
450. [illegible] F., and Dreyer, N. B.: Pharmacologic characteristics of neo- [illegible] 184, 1948.
451. [illegible] L., and Beakey, J. F.: A demand value for administration of [illegible] streptomycin. Dis. Chest, 14:386, 1948.
452. Segal, M. S., and Beakey, J. F.: Use of isuprel for management of bronchial asthma. Bull. New England Med. Center, 14:62, 1947.
453. Segal, M. S., Beakey, J. F., Bresnick, E., and Levinson, L.: Evaluation of therapeutic substances employed for relief of bronchospasm. Bull. New England M. Center, 10:21, 1948.
454. Segal, M. S., and Beakey, J. F.: Management of bronchial asthma. Use of isuprel. Ann. Allergy, 5:317, 1947.
455. Segal, M. S., Levinson, L., and Miller, D.: Penicillin inhalation therapy in respiratory infections. J.A.M.A., 134:762, 1947.
456. Sellers, E. D., and McKenzie, E.: Mold fungi in etiology of respiratory allergic diseases. VIII: Mold allergy in west Texas. Ann. Allery, 5:455, 1947.
457. Serafini, U., and Biozzi, G.: Action of Antergan on histamine curve of blood in asthmatic patients. Policlinico, 55:385, 1948.
458. Serafini, U., and Lauricella, E.: Potassium test in asthmatics. Il Progresso Médico, 4:35, 1948.
459. Serafini, U., and Biozzi, G.: Blood histamine after physical exercise in normal subjects and patients with hay fever. Clin. nuova, 2:357, 1946.
460. Serafini, U.: LaTerapia Antiallergica con un Antistaminico Sintetico, Clin. Nuov., Roma, 4:142, 1947.
461. Serafini, U.: Studies on histamine and histamine antagonists. J. Allergy, 19:256, 1948.
462. Serafini, U., and Brozzo, E.: Synthetic antihistaminic substances: effects of antergan on potassium calcium equilibrium of serum. Bull. Soc. Ital. Biol. Sper., 23:26, 1947.
463. Serafini, U., de Sanctis C. and Fabiani, F.: Blood in asthma during experimental fever. Clin. Nuova, 3:43, 1948.
464. Seltzer, A.: Convulsions following epinephrine. Report of a case. Ann. Allergy, 6:151, 1948.
465. Shapero, W., and Gwinner, M. W.: Sensitivity to thiamine hydrochloride. Ann. Allergy, 5:349, 1947.
466. Sheldon, J. M., Weller, K. E., Haley, R. R., & Fulton, J. F.: Clinical observations with decapryn. U. of Michigan Hosp. Bul., 14:13, 1948.
466-A. Shepard, W., and Philips, K. T.: Periarteritis nodosa, a case report, Connecticut State M. J., 12:316, 1948.
467. Sherman, W. B.: Drug allergy. An. J. Med., 3:586, 1947.
468. Shulman, M. H.: Prophylaxis against allergy, a pediatric program. New England J. of Med., 239:391, 1948.
469. Siegmund, O. H., Granger, H. R., and Landis, A. M.: The bronchodilator action of compounds structurally related to epinephrine. J. Pharm. & Exper. Therapeutics, 90:254, 1947.
470. Silversides, J. L.: Giant bullous emphysema. Canad. M.A.J., 57:452, 1947.
471. Simon, F. A.: Current problems in clinical allergy. Southern M. J., 40:1005, 1947.
472. Singer, J. J.: Bronchiectasis. Dis. Chest., 14:92, 1948.
473. Skouble, A. P.: Effect of antistine on allergic diseases. Nord. Med., 34:1022, 1947.
474. Slesinger, H. A.: The fate of the allergic child. Pennsylvania M. J., 51:988, 1948.
475. Sloan, J. O., Bain, G. P., and Brucer, M.: Depth of penetration of nebulized substances in the respiratory tract. Proc. Soc. Exper. Biol. & Med., 66:2641, 1947.
476. Smart, R. H.: Recent advances in pulmonary diseases. California Med., 67:293, 1947.
477. Smith, A.: "Cures" for asthma and hay fever. Life and Health, Feb., 1948.
478. Smith, C. E.: Recent medical progress in pulmonary mycotic infections. California Med., 67:179, 1947.
479. Smyth, F. S., Bowen, et al: Asthma in children. Pediatrics, 2:119, 1948.
480. Sonck, C. E.: Salvarsan asthma. Acta Allerg., K.B.H., 1:191, 1948.
481. Souders, C. R., and Kingsley, J. W., Jr.: Bronchial adenoma. New England J. M., 239: 459, 1948.
482. Soulas, A.: Bronchial syndrome according to bronchoscopic observations. Presse Méd., 55:694, 1947.

483. Southwell, N.: Anthisan in treatment of bronchial asthma and hay fever. Brit. M. J., 1:877, 1948.
484. Spain, W. C., and Pflum, F. A.: An evaluation on the present status of antihistamine substances. New York State J. Med., 48:2272, 1948.
485. Spain, W. C.: Principles of therapy in allergic diseases. Southern M. J., 41:439, 1948.
486. Spain, W. C.: Medical management of attacks of bronchial asthma. Ann. Allergy, 6:53, 1948.
487. Spatt, E. D., and Grayzel, D. M.: Cor Pulmonale. Observations on forty-two autopsied patients. Am. J. M., 5:252, 1948.
488. Spencer, G. E., and Kent, E. M.: Diagnosis and treatment of bronchiectasis. Pennsylvania M. J., 51:1122, 1948.
489. Squier, T. L.: Löffler's syndrome. Dis. of Chest, 13:609, 1947.
490. Stahl, C.: Aminophyllin therapy. Nord. Med., 34:1345, 1947.
491. Steinhausen, T. B., and Fine A.: Unsuspected bronchiectasis. Med. Radiogr., 23:254, 1947.
492. Sterling, A., Fishman, A. E., & Sharps, F.: Massive doses of penicillin in chronic asthma. Am. Pract., 2:570, 1948.
493. Sterling, A., and Hollander, B. S.: Toxic effects of B. Pyocyaneus vaccine. M. Rec., 160: 550, 1947.
494. Sternberg, L., and Gottesman, J.: Clinical observation with Thephorin. Ann. Allergy, 6:569, 1948.
495. Sternberg, L.: Psychosomatic rhinorrhea and dyspnea. New York St. J. Med., 48:639, 1948.
496. Stevenson, I. P.: Therapeutic effect of climate of Arizona. Arch. Phys. Med., 28:644, 1947.
497. Stillwell, D. E., Rimington, C., and Maunsell, K.: Allergens of house dust: comparison with products derived from molds. Brit. J. Exper. Path., 28:325, 1947.
498. Streider, J. W.: Surgical aspects of bronchiectasis. New England J. Med., 238:109, 1948.
499. Stroh, J.: Northwest Pollens. Ann. Allergy, 5:337, 1947.
500. Sulzberger, M. B., and Baer, R. L.: Office immunology including allergy. J.A.M.A., Oct. 11, 1947.
501. Swanton, C.: Asthma and other psycho-physical interrelations. M.J. Australia, 1:138, 1947.
502. Sweany, H. C., and Thompson, J. R.: Laboratory methods useful in differential diagnosis of chronic chest diseases. Illinois Med. J., 94:189, 1948.
503. Sweigert, C. F., McLaughlin, E. F., and Heath, E. M.: Carcinoma of pancreas with pulmonary lymphatic carcinomatosis simulating bronchial asthma. Ann. Int. Med., 27:301, 1947.
504. Taplin, G. V., and Bryan, F.: Use of micronized therapeutic agents by inhalation. Ann. Allergy, 6:42, 1948.
505. Taub, S. J.: Asthma. M. Clin. N. Am., 33:230, 1948.
506. Tell, N.: Management of allergic patient. Hawaii M. J., 7:34, 1947.
507. Telles, W.: Tropical [illegible] Hosp. Rio de Janeiro, 31:759, 1947.
508. Thibergc, N. F.: [illegible] in bronchiectasis. Southern M. J., 41:873, 1948.
509. Thomas, D. R., Jr., [illegible] W.: Handling of certain emergency allergic conditions. Southern M. J., 40:670, 1947.
510. Tichenos, C. J., and Lafsky, B. P.: Asthma. Report of a fatal case. Clin. Proc. Child. Hosp., Wash., D. C., 3:50, 1947.
511. Tiffenau, R., and Singuier, J.: Delayed absorption of aerosols. Bull. Acad. Nat. Méd., 131:697, 1947.
512. Tillisch, J. H., and Guilford, F. R.: Medicine in aviation. Am. J. M., 4:633, 1948.
513. Tourenc, R.: Bronchial asthma treated by bilateral stellectomy. Méd Trop., 7:159, 1947.
514. Trethewie, E. R.: Age and lung histamine. J. Immunol., 56:211, 1947.
515. Truitt, E. B., Jr., Carr, C. J., Bubert, H. M., and Krantz, J. C., Jr.: Quantitative estimation of theophyllin in blood. J. Pharm. & Exper. Therap., 91:185, 1947.
516. Tuft, L.: Newer antihistaminic drugs in treatment of allergic states. Am. Practitioner, 2:1, 1947.
517. Tuft, L., Blumstein, G. I., and Heck, V. M.: Pulmonary function in bronchial asthma. J. Allergy, 19:288, 1948.
518. Unger, L.: Annual critical review of the recent literature on bronchial asthma. Ann. Allergy, 2:49, 1944.
519. Unger, L.: Annual critical review of the recent literature on bronchial asthma. Ann. Allergy, 3:133, 1945.
520. Unger, L.: Annual critical review of the recent literature on bronchial asthma. Ann. Allergy, 4:299, 1946.
521. Unger, L., and Gordon, B. F.: Bronchial asthma. (IV). Critical review of literature. Ann. Allergy, 6:64-93, 159-177, 1948.
522. Unger, L., Levy, H. A., Unger, A. H., and Eisele, I. B.: Diagnosis and treatment of bronchial asthma. Postgraduate Med., 4:62, 1948.
523. Unger, L.: Differential diagnosis and management of bronchial asthma. Postgraduate Med., 3: April, 1948.
524. Vall, R. A.: Casos de pequeña alergia, Larvada o Manifiesta. Medicina Clinica, Barcelona, 1:No. 6.
525. Valledor, T., and Rodriguez Diaz: Bronchiectasis in infancy and surgical treatment. Study of five cases with lobectomy. Rev. Cubana Paediat., 18:51, 1946.
526. Vallery Radot, P., Hamburger, J., and Halpern, B.: Activité therapeutiques des dérivés de la Thiodiphenylamine dans les états allergiques. La Sem. des Hopitaux de Paris, 24:655, 1948.
527. Vallery Radot, P., Blamoutier, P., and Halpern, B.: In which types of asthmas do antihistaminic drugs have an action? La Semain des Hopitaux de Paris, 24:2553, 1948.
528. Vallery Radot, P., Hamburger, J., and Halpern, B.: Activité therapeutique des dérivés de la Thiodiphenylamine dans les états allergiques. La Semaine des Hopitaux de Paris, 24: 21, 1948.
529. Vallery Radot, P., Hamburger, J., and Halpern, B.: A new synthetic antihistamine drug. Presse Méd., 58:661, 1947.
530. Vallery Radot, P., and Blamoutier, P.: X-ray treatment of asthma. La Presse Médicale, 56:68, 1948.
531. Van Vaerenberg, G.: Roentgen ray treatment of bronchial asthma. Belg. Ars. Medici, 2:723, 1947.
532. Van Wezel, N.: Pulmonary tuberculosis and allergic asthma. Ann. Allergy, 6:54, 1948.
533. Vaughan, W. T., and Black, J. H.: Practice of allergy, J.A.M.A., Nov. 20, 1948.
534. Veach, O. L.: Aerosol treatment with penicillin and streptomycin. Rocky Mt. M. J., 44: 816, 1947.

535. Veldee, M. V.: Specifications recommended as guides in the collection and preservation of pollens. Ann. Allergy, 6:56, 1948.
536. Villafane Lastra, T., and Bai, A.: Allergic pictures of chronic brucellosis with special reference to nasal and bronchial asthma. Revista Méd de Córdoba, 35:263, 1947.
537. Villanova, P.: Lethal asthmas. Presse Méd., 56:828, 1948.
538. Vilar Bonet, J.: Inhalational therapy in respiratory diseases. Med. Clinica, 10:257, 1948.
539. Von Heni, F., Thedering, F., and Riethmüller, H. U.: Transitory pulmonary infiltrations with eosinophilia. Deutsche Med. Wchnschr., 72:421, 1947.
540. Wakefield, H., and Hirsch, E. F.: Unexpected death with bronchial asthma. Illinois M. J., 92:187, 1947.
541. Waldbott, G. L., and Borden, R.: Clinical evaluation of Neohetramine. Ann Allergy, 6:305, 1948.
542. Waldbott, G. L.: Las Drogas antihistaminicas. Medicina Mex., 27:193, 1947.
543. Waldbott, G. L., and Young, M. L.: Antistine, Nro Antergan, Neohetramine, Trimeton, an Appraisal. J. Allergy, 19:313, 1948.
544. Waldbott, G. L.: The antihistamine drugs. J.A.M.A., 135:207, 1947.
545. Waldbott, G. L., Shea, J. J., and Harrington, M. M.: Adequate diets in advanced chronic asthma. Ann. Allergy, 6:372, 1948.
546. Walker, J. S., and Gann, E. L.: Laryngeal edema in epidemic parotitis. Ann. Otol., Rhin. & Laryng., 57:163, 1948.
547. Walker, R. H.: Fatal anaphylaxis following typhus vaccine injection. U. S. Nav. M. Bull., 48:303, 1948.
548. Walsh, M. N., and Kierland, R. R.: Psychotherapy in treatment of neurodermatitis. Proc. Staff Meet. Mayo Clinic, 22:378, 1947.
549. Walton, C. H. A.: The new antihistamines. Canad. M.A.J., 57:315, 1947.
550. Walzer, E. H., Sherman, J., Chait, R. A., and Walzer, M.: Survey of ragweed pollination in New York metropolitan district in 1946. New York State J. Med., 47:1979, 1947.
551. Ward, A. T., Jr., Livingston, S., and Moffat, D. A.: Asthma in children. Treatment with the radium nasopharyngeal applicator. Miss. Valley M. J., 69:114, 1947.
552. Warren, I. S., and Dixon, F. J.: Antigen tracer studies and histologic observations in anaphylactic shock in guinea pigs. Amer. J. Med. Sc., 216:136, 1948.
553. Wasson, U. P.: Ethylene disulphonate and the allergic state. Med. Rec. N. Y., 160:471, 1947.
554. Wearing, J. D.: Bronchiectasis simulating chronic bronchitis: Study of 46 cases. Lancet, 1:822, 1948.
555. Weiss, E.: Psychosomatic aspects of allergic disorders. Bull. N. Y. Acad. Med., 23:604, 1947.
556. Weiss, W. I., and Howard, R. W.: Antihistamine drugs in hay fever. J. Allergy, 19:271, 1948.
557. Whittemore, A. L., Jr., and De Gara, P. F.: Sulfadiazene sensitivity. An Unusual Case, J. Allergy, 18:382, 1947.
558. Williams, E. B., Jr., and Walker, W. H.: Loffler's syndrome with brief review of literature. J. Nat. M. Assn., 39:211, 1947.
559. Wilson, H. T. H.: Tropical eosinophilia. Brit. M. J., 1:801, 1947.
560. Wiswell, J. G., and Raekemann, F. M.: Chemical factors in asthma. New England J. Med., 237:364, 1947.
561. Wittich, F. W.: Trimeton in treatment of allergic diseases. Ann. Allergy, 6:497, 1948.
562. Wittich, F. W.: Comment on paper by Pierce and Mothersill. Quart. Rev. All. and Appl. Immun., 1:430, 1947.
563. Wolf, F. A., and Wolf, F. T.: The Fungi, 448 pp. New York: John Wiley & Sons, 1947.
564. Wyrens, R. J.: Aminophyllin in treatment of asthma. Nebraska M. J., 32:273, 1947.
565. Yegge, W. B.: Diagnostic problem of silicosis. Dis. of Chest, 14:550, 1948.
566. Zeller, M.: An unusual effect of aminophyllin on the intestinal tract. Ann. Allergy, 3:369, 1945.
567. Zeun, W.: Collapse therapy of asthmatic tuberculous patients. Schweiz. Ztschr. Tuberk., 4:169, 1947.
568. Zohn, B.: Skin testing with fractions of chocolate. Ann. Allergy, 5:344, 1947.
569. Zussman, B. M.: Bronchial asthma and allergy. Memphis M. J., 22:177, 1947.
570. Zivitz, N.: Importance of predisposing and contributory factors in an allergic evaluation. J. Florida M. A., 34:447, 1948.
571. Hughes, R. F.: Clinical experience with Antistine. Ann. Allergy, 6:405, 1948.
572. Hughes, R. F.: New therapeutic approaches in allergy. Canad. M. A. J., 57:323, 1947.
573. Hunter, R. B., and Dunlop, D. M.: Antihistamine drugs in asthma. Lancet, 1:474, 1948.
574. Castex, M. R., Mazzei, E. S., Remolar, J. M., and Pedace, E. S.: Letter, J.A.M.A., Jan. 24, 1948.
575. Arner, B.: Antihistamine treatment in allergic diseases. Nord. Med., Stockholm, 39:1386, 1948.

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News Items

FROM THE TECHNICAL INFORMATION OFFICE OF THE SURGEON GENERAL

A release dated July 1, 1949, from the Department of the Army, Office of the Surgeon General, Technical Information Office, Washington 25, D. C., sketches 174 years of military medicine, beginning in 1775. The sketch has been placed in the College library.

Major General R. W. Bliss, Surgeon General of the Army, also announces the joint staffing of four Naval hospitals with Army medical personnel at St. Alban's Hospital, Long Island, New York; Corona and Long Beach Hospitals, California; and Portsmouth Hospital, Portsmouth, Virginia.

It is also announced that 486 medical school graduates and senior medical students have been selected for the Military Intern and Civilian Intern Programs, and began their internships and training July 1.

Commissions as first lieutenants in the Medical Corps Reserve have been given to 231 medical school graduates who will be assigned to Army general hospitals taking part in the Military Intern Program. These internships are offered each year by the Army to selected graduates of medical schools approved by the American Medical Association. Appointments begin on July 1 of each year and terminate June 30 the following year. Commissions in the Regular Army are tendered to some at the close of the year.

THE HEBREW MEDICAL JOURNAL

Volume 1, 1949, of *The Hebrew Medical Journal* has been received for the College library. This volume initiates the twenty-second year of publication of this bi-lingual, semi-annual journal, edited by Moses Einhorn, M.D. The journal is a contribution to the development of Hebrew medical literature and terminology, so important now with the establishment of the Hebrew University-Hadassah Medical School. A number of articles dealing with present health conditions in Israel are presented in this issue. Included is a paper on infectious diseases in that country, by Moshé Fischel, M.D., of Tel Aviv, in which he discusses the most prevalent diseases, such as malaria, typhus and dysentery.

QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

Effective with the publication of the June, 1949 issue, through the approval of the Board of Regents, the *Quarterly Review of Allergy and Applied Immunology* will be published under the auspices of The American College of Allergists. The domestic subscription rate to subscribers of the ANNALS is $5.00, making a club rate of $11.00 for the two journals. Otherwise, the *Review* is obtainable at the rate of $6.00 per year. Foreign rates are $1.50 more.

OHIO VALLEY ALLERGY SOCIETY

At the meeting of the Ohio Valley Allergy Society May 14 and 15, the following officers were elected for the coming year: President, L. E. Seyler, M.D., Dayton, Ohio; President-Elect, C. B. Bohner, M.D., Indianapolis, Indiana; Secretary-Treasurer, D. J. Parsons, M.D., Springfield, Ohio. Dr. A. R. Zoss of Cincinnati gave a paper on the use of bronchoscopy in asthmatic patients, and Dr. Milton Rosenbaum, Associate Professor of Psychiatry at the University of Cincinnati, gave a paper on psychosomatic factors in allergy.

The next meeting of the Ohio Valley Allergy Society will be held in Lexington, Kentucky, in October.

SWEDISH ASSOCIATION FOR ALLERGOLOGY

The new members of the Board of the Swedish Association for Allergology, who were elected April 20, 1949, are: Professor Sven Hellerström, Chairman; Professor Gösta Dohlman, Vice Chairman; Dr. Birgitta Sundberg, Treasurer; Dr. Sven Kraepelien, Secretary. The other members of the Board are Head Physician Olof Wilander, Head Physician Gösta Änggård, and Docent Åke Nilzén. All correspondence to the Association should be addressed to Professor Sven Hellerström, Karolinska Sjukhuset, Stockholm 60, Sweden.

THE CUBAN SOCIETY OF ALLERGISTS

We are very happy to announce that the Cuban Society of Allergists has been established and that the Board of Directors for the year 1949 is as follows: President, Dr. Gonzalo Estrada de la Riva; Vice President, Dr. Jose Cadrecha Alvarez; Secretary, Dr. Jose M. Quintero Fossas; Treasurer, Dr. Jose Pedrera Rodriguez. Members of the Board: Dr. Julio de los Santos, Dr. Josefina Amiguet Villagrasa, and Dr. Javier Fernandez de Castro.

The new society has already accepted membership in the International Association of Allergists, so that now the International Association numbers fifteen national allergy societies as members.

The College wishes to congratulate the outstanding allergists of Cuba upon organizing the Cuban allergists and extends every wish for its continued progress.

BRAZILIAN INSTITUTE OF HISTORY AND MEDICINE

At a special session of the Brazilian Institute of History and Medicine held November 11, 1948, there was an election of a new Board of Directors who will hold office for the period beginning May 17, 1949, until 1951. Those elected to office are as follows: President, Dr. Ivolino de Vasconcellos (re-elected); 1st Vice President, Dr. Paulo Arthur Pinto da Rocha; 2nd Vice President, Prof. Alvaro Doria; Secretary-General, Dr. Ordival Gomes; 1st Secretary, Dr. Severino Cabral Sombra; 2nd Secretary, Dr. Mario Ferreira Franca; Speaker, Dr. Jayme Mendonca Castro; 1st Treasurer, Dr. Armando R. Bandeira; 2nd Treasurer, Prof. Antonio Carlos Villanova; Director of Museum, Dr. Ary Luiz de Menezes; Director of Library, Prof. E. M. Salles Cunha; Director of Archives, Prof. Newton Guimaraes Alves; Director of Reports, Dr. Paulo R. Bandeira; Director of Publications, Dr. Oscar D'Utra e Silva.

On May 17, 1949, in the Assembly Hall of the General Polyclinic of Rio de Janeiro, the Brazilian Institute held its annual meeting and presented the following special program:

Part 1.—Election of the Boards of Directors. The former Director of the Institute, Prof. Jose Messias de Carmo, spoke regarding the election. Also, the speaker for the new Board of Directors, Dr. Jayme Medonca Castro, spoke.

Part 2.—Bicentennial Commemoration of Edward Jenner. Doctor Vasconcellos spoke to the assembly about the life and work of this distinguished scholar.

* * *

We are pleased to announce that "Allergy," Second Edition, by Urbach and Gottlieb, published by Grune and Stratton, Inc., is now available because of another printing. Many allergists seem to have obtained the impression that this edition is no longer available.

* * *

Frank L. Rosen, M.D., has announced the moving of his office to the Professional Building, 32 Johnson Avenue, Newark, New Jersey.

BOOK REVIEWS

DISEASES OF THE ADRENALS. By Louis J. Soffer, M.D. 304 pages. Illustrated with 42 engravings, 2 colored plates. Cloth. Price $5.50. Philadelphia: Lea and Febiger, 1946.

Our developing knowledge of the chemical and physiological processes revealing the significance and function of the adrenals is well crystalized and brought to date in this text.

With clarification of our knowledge of adrenal physiology, the pathway is opened in our approach to the clinical and functional problems associated with the other endocrine glands.

The information gathered in this volume combines the results of many authoritative investigators the world over with the authors's own laboratory studies.

There are ten volumes, including the anatomy, morphological structure, and embryology of the adrenals; chemical and mechanical techniques important in the diagnosis of adrenal cortex disease; physiology of the adrenals; Addison's disease, its treatment; adrenogenital syndrome; blood electrolyte and hormonal studies; sympathogoniomas, neuroblastomas and ganglioneuromas of the adrenal; and pheochromocytomas and paragangliomas of the adrenal.

The allergist will obtain much basic information since "the physiology of the adrenal medulla is essentially a study of the pharmacology of epinephrine."

The book is comprehensive, concise, practical and clearly written.

CLINICAL ALLERGY. New (2nd) Edition. By Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia. 690 pages, 54 illustrations, and 3 plates in color. Price $12.00. Philadelphia: Lea & Febiger, 1949.

This long-sought second edition fully meets one's expectations. As it has been over ten years since the first edition appeared and other symptom complexes and syndromes are now recognized as being due to super-sensitiveness, the author in the second edition brings the book up to date. The author adheres to the primary purpose of his first edition of writing a book primarily for the general practitioner, hoping also that it may be useful to the medical student, to those beginning the study of allergy, and even to specialists in branches of medicine in which allergy is considered to play a part. The data are concise, exhaustive reviews or statistical reports having been eliminated. Instead of an extensive bibliography, the author adheres to the more recent method of listing books or publications thought valuable for reference purposes.

Two new chapters have been added, one on allergy to fungi and the other a discussion of allergy to inhalants other than pollens and molds. The entire book has been revised and modified so that the present-day knowledge of allergy can be clearly understood by the practicing physician. New illustrative case reports have been added.

The volume is durably bound, and the illustrations are unusually clear.

KOMPENDIUM DER PARASITISCHEN WORMER IM MENSCHEN (Compendium of Parasitic Worms in Man). By Dr. Hans A. Kreis, Privatdozent der Parasitologie an der Universitat Bern, Bern Switzerland. With a Forward by Dr. P. Vollenweider, Direktor des Eidg. Gesundheitsamtes, Bern Switzerland. 136 pages, with 70 figures. Price: Bound, Fr. 10. Basel: Benno Schwabe & Co., 1947.

This book, written in German, is very informative and is a complete treatise on the subject of worm in man. It is divided into four sections.

The first section consists of five chapters dealing with an historical sketch of the early observers of parasites and the nature of parasites. One chapter consists of the structure, development and biology of the worms infesting man—the Trematoda, Cestoda, and Nematoda. Another chapter treats the general manifestations of Helminth infestations.

The second section, consisting of five chapters, presents the authoritative and most recent procedures for the diagnoses of Helminthiases. This section gives the seriologic diagnosis, as well as the examination for the stools, urine, blood, connective tissue, et cetera. The last chapter in this section profusely illustrates the characteristic structure of the various worms, and their comparative sizes, including their ova, so that the student could very readily recognize them.

The third section, consisting of three chapters, discusses the incidence and geographical distribution of the Trematoda, Cestoda, and Nematoda, as well as their pathology, incubation period, intermediary host, period of proliferation, therapy, prophylaxis, and prognosis. There is also a detailed evaluation of the various medications used in the treatment of worms.

The final section presents the classification of the various worms with tables giving detailed measurements and other methods of recognition, and other valuable references on authoritative textbooks on Helmintology.

It is interesting that in those countries where infestation with worms is common that eosinophilia is not considered by many of much diagnostic importance in allergic diseases. However, with our developing knowledge of the potent antigens in some of these worms, the degree of eosinophilia may be a rough index of the degree of hypersensitiveness acquired by a patient infested, particularly those with an allergic background. In those countries where cytological studies of nasal smears of the blood and sputum and less frequently of the urine and stools are made by allergists routinely, they should be on the alert for worm infestation where the eosinophilia counts are unusually high.

This little book is a valuable reference book on the subject of worm infestation which is so frequently overlooked by the average physician in his practice.

THE ESSENTIALS OF ALLERGY. By Francisco J. Farrerons-Co., M.D., Jefe del Departamento de Alergia del Hospital del Sagrado Corazon, Ayudante H. del Instituto Espanol de Fisiologia y Bioquimica del Consejo Superior de Investigaciones Cientificas, Barcelona, Spain, with an Introduction by F. W. Wittich, M.D. 450 pages, 67 figures with a colored plate. Barcelona: J. M. Masso, 1948.

This book is printed in Spanish with the exception of the Introduction (which is in both English and Spanish), and Chapter 21 (which is in English), It is composed of four Sections and an Appendix. The author is internationally known for his contributions not only to allergy but to physiology and biochemistry.

Section One presents the history, definition and the discussion of the fundamentals of allergy. The Second Section classifies in detail the various allergens. Section Three deals with other factors which influence the allergic phenomena and indicate the broad knowledge of the subject by the writer. The Fourth Section presents the diagnosis and treatment of the allergic diseases involving the various domains of the body. The Appendix (Chapter 21) contains an excellent suggestion for the universal classification and terminology of allergic diseases which the author presented at the Annual Meeting of The American College of Allergists in San Francisco, June 28, 1946.

Various techniques are described and the author gives due credit to those who have contributed to literature on allergy. It is a very compact book and should be read by all Spanish-speaking allergists. It is to be regretted that it is not given a complete English translation.

1949 CURRENT THERAPY. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., with Twelve Consulting Editors and 243 Contributors. 672 pages, and numerous tables. Price, $10.00. Philadelphia and London: W. B. Saunders Co., 1949.

This is a new annual volume which is different both in concept and in content from any other book ever published. Although only a few months old, it is now going

into its second printing. The reader has readily available a detailed and unbiased report on the very latest treatments for every disease and condition he is likely to encounter, whether frequent or rare. It is the best treatment available today for that particular disease, according to the Board of Consultants who selected each Contributor as an authority with practically the most effective treatment for any disease in question. Nothing is presented which is experimental or comprised of excerpts from the literature. Each article was written especially for this book and represents the actual working report of a foremost authority describing the method he is using in his practice at the present time.

The book is attractively bound, has an easy-to-read two-column style on a large page in clear type, and is arranged in fourteen convenient sections. Each section is prefaced by a "Contents" page listing alphabetically the diseases that are to be found therein.

Any practicing physician or specialist in any field will find this book one of the most convenient, ready reference books on therapy on his desk.

1948 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. By Marion B. Sulzberger, M.D., Professor of Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center; Director of Department of Dermatology and Syphilology, New York Skin and Cancer Unit, New York, and Rudolf L. Baer, M.D., Assistant Professor of Clinical Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center, New York. 560 pages, 72 figures. Price, $5.00. Chicago: The Year Book Publishers, 1948.

These well-known authors have again contributed a complete up-to-date Year Book which gives concise, critical accounts of authoritative literature which has appeared during the year on the subject of dermatology and syphilology. The authors stress the leadership which dermatology and syphilology have assumed following the war. There are thirteen chapters furnishing convincing proof that dermatologic studies continue to contribute to all basic branches of medical science. For example, this book contains reports on the following investigations in which the skin was used as test tissue; psychiatric and neurologic studies; processes of maturation and aging (geriatrics); basic problems of the effects of climate and environment; actions of physical agents and hormones; mechanisms of cancer production; fluid exchange and vascular function; vascular alterations in essential hypertension; effects of sympathetic-mimetic and cholinergic drugs and their mechanisms as observed in the structures and responses of the skin; biochemical bases of carbohydrate and lipid metabolism and of pigmentary changes; modes of action of histamine, antihistaminics, hyaluronidase and other spreading factors; several mycologic and bacteriologic problems related to the skin; immunologic relationships and factors influencing resistance and susceptibility to disease.

Under the general subject "Eczematous Eruptions of the Hands," the authors in their masterful way present the allergic etiology in detail and its relationship to other skin conditions with concise directions for management of the conditions, including cleansing agents, protective devices, bandages, and systemic antipruritic mixtures. Prescriptions for topical therapy are numerous.

Chapter 1 on "Treatment and Prevention (Exclusive of Venereal Diseases)" presents the more recent results of therapy with Penicillin, Bacitracin, the treatment of superficial fungous infections in routine dermatologic practice, and the newer remedies used in the therapy of mycoses of the feet and the treatment of many other skin diseases. There is an excellent chapter on eczematous dermatitis and urticaria (allergic and nonallergic), as well as a very good chapter on drug eruptions.

The authors have shown exceedingly well in this latest review the great importance of the fundamental knowledge of dermatological diseases and their reduction and alleviation of suffering. The illustrations very clearly define the lesions.

"In the asthmatic cases, both those with asthma due to pollen and those having asthma from other sources, the figures of the effectiveness of the drug [Hydryllin] are more impressive than those of other antihistaminics."

Report of Committee on Therapy to the American Academy of Allergy, St. Louis, Dec. 15-17, 1947.

The choice of Hydryllin in asthma and other allergic manifestations is based on its clinical effectiveness in a large series of cases, and also on its relative freedom from side reactions. Because of its safety, Hydryllin may usually be employed day and/or night, and over prolonged periods of time.

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Available as follows:

HYDRYLLIN Tablets—
Each tablet contains:
Diphenhydramine (Searle)..... 25 mg.
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One-half gram quantities at 70% of gram prices

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with an allergen and subsequent release of histamine is considered to be the mechanism of allergic disorders.

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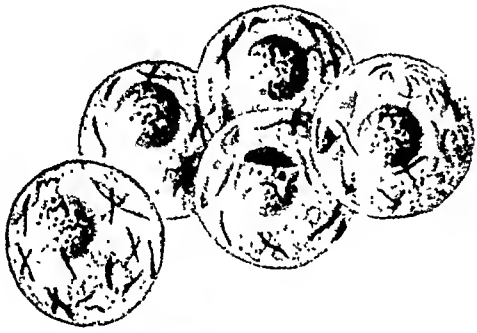

BENADRYL, blocking the action of histamine, prevents reaction in cells that have been sensitized. Relief of symptoms is gratifyingly rapid, usually occurring within an hour or two after the first dose. And treatment with BENADRYL is simple, convenient, and inexpensive.

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BENADRYL has been found highly effective in a wide variety of allergic states, ranging from seasonal, such as hay fever, to the non-seasonal, such as acute and chronic urticaria, angioneurotic edema, vasomotor rhinitis, contact dermatitis, erythema multiforme, pruritic dermatoses, dermographism, serum sickness, food allergy, and sensitization to drugs, such as penicillin and the sulfonamides.

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Allergy	Total Cases	No. Benefited	% Benefited	% Side Reactions
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Vasomotor Rhinitis	133	87	65.4	8
Asthma	189	82	43.3	6
Urticaria	48	39	81.2	11.5
Angioneurotic Edema	12	8	66.6	0
Contact Dermatitis	18	12	66.6	7.6
Atopic Eczema	17	14	82.3	40
Serum Sickness	3	3	100.0	0
Migraine	10	7	70.0	25
Allergic Headache	5	3	60.0	0
Drug Allergy	2	2	100.0	0
	999	644	64.5	10.9

Here's the Evidence

---based on clinical findings in 999 cases

NEOHETRAMINE® IS EFFECTIVE. It is useful in many patients in whom other antihistaminics produce marked sedation or other undesirable side-effects in the management of hay fever and other allergic disorders.

NEOHETRAMINE IS LESS TOXIC than other available antihistaminics; its lower toxicity is quantitatively more pronounced than its lower effectiveness.

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Tablets: 25 mg., 50 mg., 100 mg., Syrup—6.25 mg. per cc.—bottles of 1 pint and 1 gallon.

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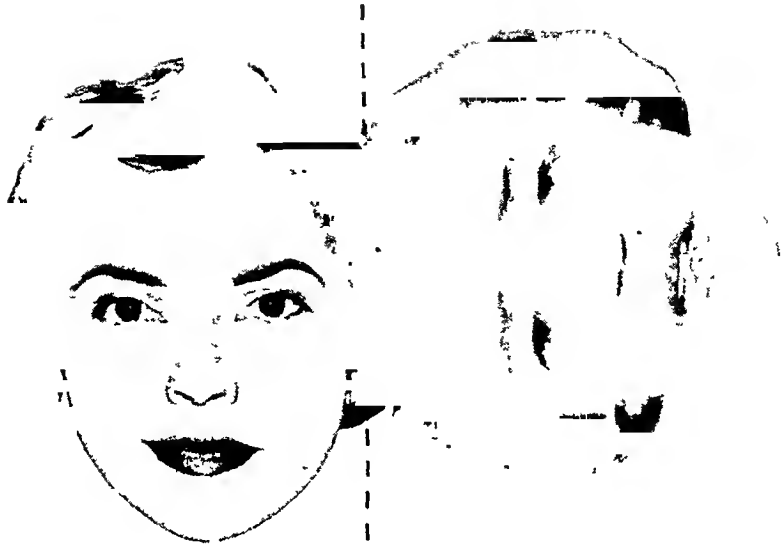

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85%–90% effective relief in over 1400 patients during an exacting 8-year clinical study.

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1—Hamel, F. K. Ann. Allergy 5:397, 1947.

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A-Fil contains 5% Menthyl Anthranilate (Menthyl Orthoaminobenzoate) and 5% Titanium Dioxide. Spectrophotometric measurements indicate the 5% Menthyl Anthranilate alone filters out over 95% of the short wave-lengths between 2950 and 3200 Angstrom Units. This is the range commonly accepted as the causative factor in sunburn and a number of other types of sensitivity to sunlight.

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Extensive clinical investigations in those regions where sunlight rich in short UV rays prevails have shown A-Fil to be highly effective. No cases of sensitivity to A-Fil have been reported. A neutral-tinted vanishing cream type preparation, A-Fil blends smoothly with the natural skin coloring.

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1 Gay, L N, and Long, J W Clinical Evaluation of Isopropylepinephrine In Management of Bronchial Asthma J A M A, 139 453, Feb 12, 1949

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Prompt, Safe, Symptomatic Relief in HAY FEVER

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Significantly, this symptomatic relief of allergic manifestations was effected with a relatively low incidence of undesirable side effects.

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1. Brewster J. M., U. S. Naval Med. Bull. 49: 1–11, January-February, 1949

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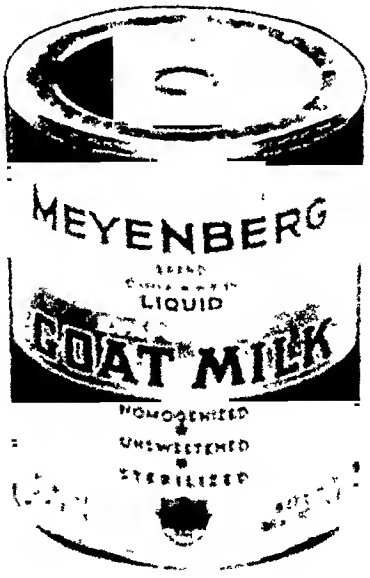

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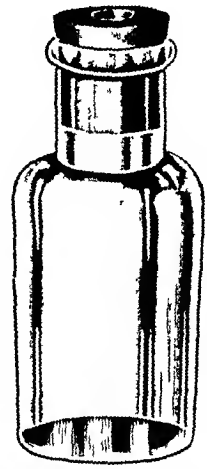

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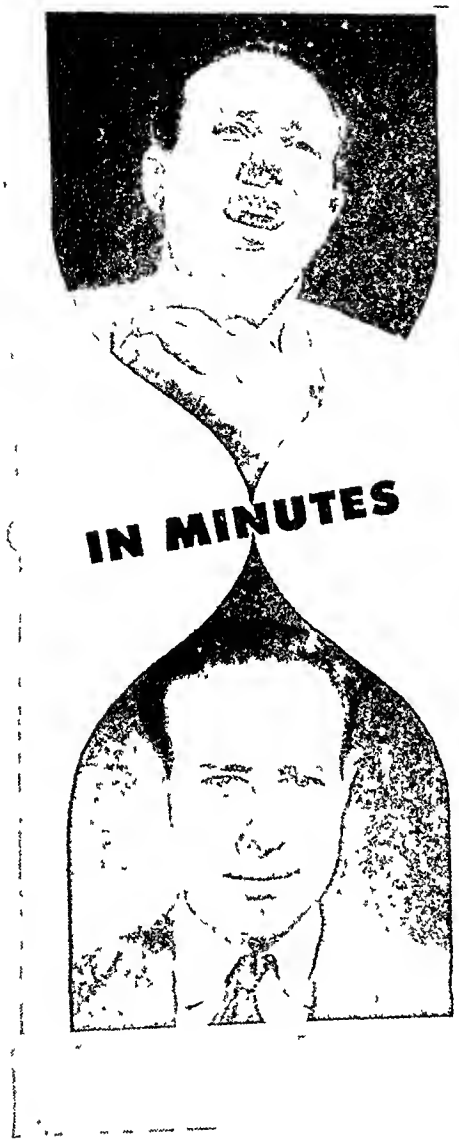

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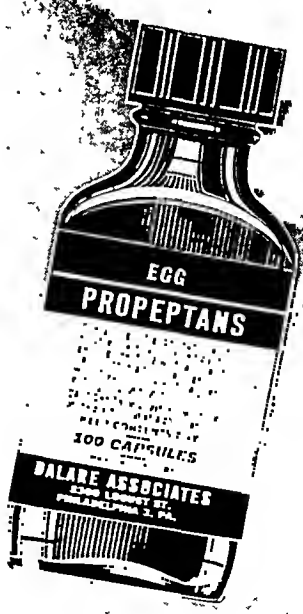

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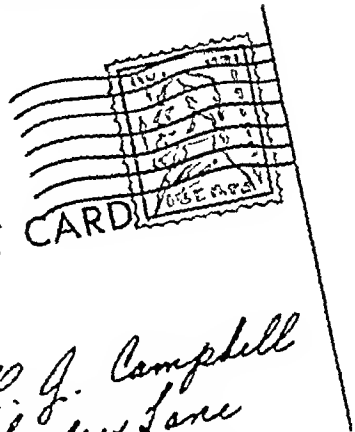

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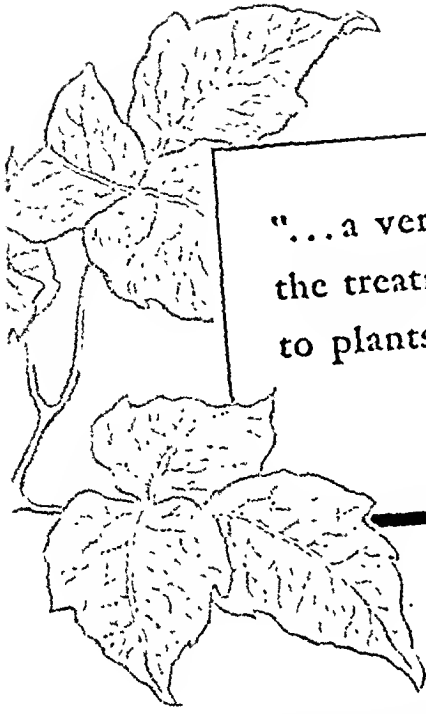

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1. Carrier, B. E., Krug, L. S., and Glenn, H. B.: J. Lancet, 68: 240, June 1948.
2. Feinberg, S. M. and Bernstein, T. B.: J. of A.M.A., 134: 10, July 1947.

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

IX. Further Studies with Mold Extracts

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IN previously evaluated extracts, consideration was given to certain modifications of the mold material prior to extraction, to subsequent treatment of a preliminary aqueous extract, and even to the culture broth itself.[1,2] In the spring of 1945, the preparation and study of more experimental extracts of *Alternaria tenuis* were undertaken. These were prepared from Alternaria grown in malt extract broth (Difco), which medium has been used throughout all our work since 1939.

PREPARATION OF EXTRACTS 13-32

The detailed technique of preparing the extracts studied will be the subject of a separate communication. In general, to a preliminary aqueous extract were added successive equal volumes of cold acetone. Even though precipitation was usually immediate after each addition of acetone, the mixtures were allowed to stand in the cold (—20° C.) for twenty-four hours for complete reaction before separation in a refrigerated centrifuge. Most precipitation occurred at 50 and 75 per cent by volume acetone concentration, but faint additional precipitate could be detected even after 93 per cent acetone concentration had been exceeded. Grossly, the precipitates usually appeared as fine to coarse flocculent, or "oily," occasionally gummy. The flocculent precipitates were in general lighter in color than those with

From the Department of Botany and Bacteriology, The University of Texas, in collaboration with The Association of Allergists for Mycological Investigations.
Assisted by a Grant-in-Aid from the Alumni Research Fund of the Society of Sigma Xi.
Dr. Morrow is an Honorary Member of the American College of Allergists.

TABLE I. TESTS WITH EXTRACTS 13-32

Ext. No.	Type of Precipitate	% Acetone by Volume	INTRADERMAL TESTS 1/100,000 Patients Tested	Reaction	%	1/10,000 Tested	Reaction	%	1/1,000 Tested	Reaction	%	1/100 Tested	Reaction	%	PUNCH (SCRATCH) 1/50 Tested	Reaction	%
A13	oil	50	38	20	48	37	32	87	36	32	89	22	21	95	10	8	80
14	floc.	75x75x50	32	13	11	31	20	65	38	25	66	25	23	92	10	1	10
15		75x75x75	30	8	27	29	12	41	39	10	19	25	23	92	10	3	30
32	oil	75x75x87	18	1	7	17	1	6	13	4	31	11	5	45	4	2	50
17	oil	75x87	30	1	3	31	6	20	39	11	11	26	20	77	10	1	10
19	oil	75x93	30	2	7	29	6	20	39	10	26	29	18	69	10	1	10
16	oil	87	30	2	7	29	2	7	39	5	13	26	10	38	10	1	10
20	floc.	87	30	2	7	29	1	3	39	7	18	26	12	46	10	0	0
18	oil	93	30	2	7	29	0	0	39	3	8	26	14	54	10	0	0
B21	floc.	50	30	9	30	29	15	52	37	19	51	25	21	81	10	0	0
23	oil	75x50	30	6	20	29	11	18	38	18	47	25	20	80	10	1	10
22	crystals	75x50	30	2	7	29	3	10	38	8	21	26	12	46	10	0	0
24	floc.	75x50	30	2	7	29	4	11	38	3	8	26	13	50	10	0	0
28	floc.	75x75	18	3	17	17	10	59	11	10	71	11	10	91	4	3	75
29	oil	75x75	18	0	0	17	1	6	13	4	31	11	4	36	4	3	75
30	floc.	75x87	18	4	22	17	6	35	14	10	71	11	6	55	4	3	75
31	oil	75x87	18	0	0	17	2	12	13	2	15	11	3	27	4	4	100
25	oil	87	30	2	7	29	3	10	38	5	13	25	11	44	10	0	0
26	floc.	87	30	0	0	29	0	0	38	2	5	26	10	39	10	0	0
27		93	30	4	13	29	5	17	38	0	0	26	13	50	10	0	0

x—Re-precipitated

the dark brown oily appearance. Whereas the flocculent precipitates usually appeared immediately, the oily material often began as an opalescent appearance of the supernatant, from which minute globules eventually began to settle out; after centrifugation, the oily precipitates formed a stratum on the bottom, leaving the supernatant clear. Sometimes both an oily and flocculent precipitate occurred simultaneously but could be stratified by repeated centrifugation, following which the oily layer could be decanted along with the supernatant, and separated from the latter in a separatory funnel. After aqueous solution some precipitates were further fractionated by re-precipitation. In this manner nine precipitates were obtained. (*A*, Table I).

Following a slightly modified technique another preliminary aqueous extract was separated into eleven acetone-precipitable fractions. In this series further separation of more of the re-dissolved precipitates was accomplished. (*B*, Table I).

After removal of all acetone the precipitates were dissolved in a minimal amount of water and distributed to tared Erlenmeyer flasks in which they were quick-frozen and dried by lyophilization. The dried material was dissolved in Hollister-Stier solution in a ratio of 1/50, and sterilized by Seitz filtration. The extracts thus prepared were denoted by numbers 13 to 32, and distributed to our membership for skin testing on Alternaria-sensitive patients.

SKIN TESTING WITH EXTRACTS 13-32

In Table I are shown the results of direct skin testing by both the punch (scratch) and intradermal methods. Skin reactive principles are seen to be

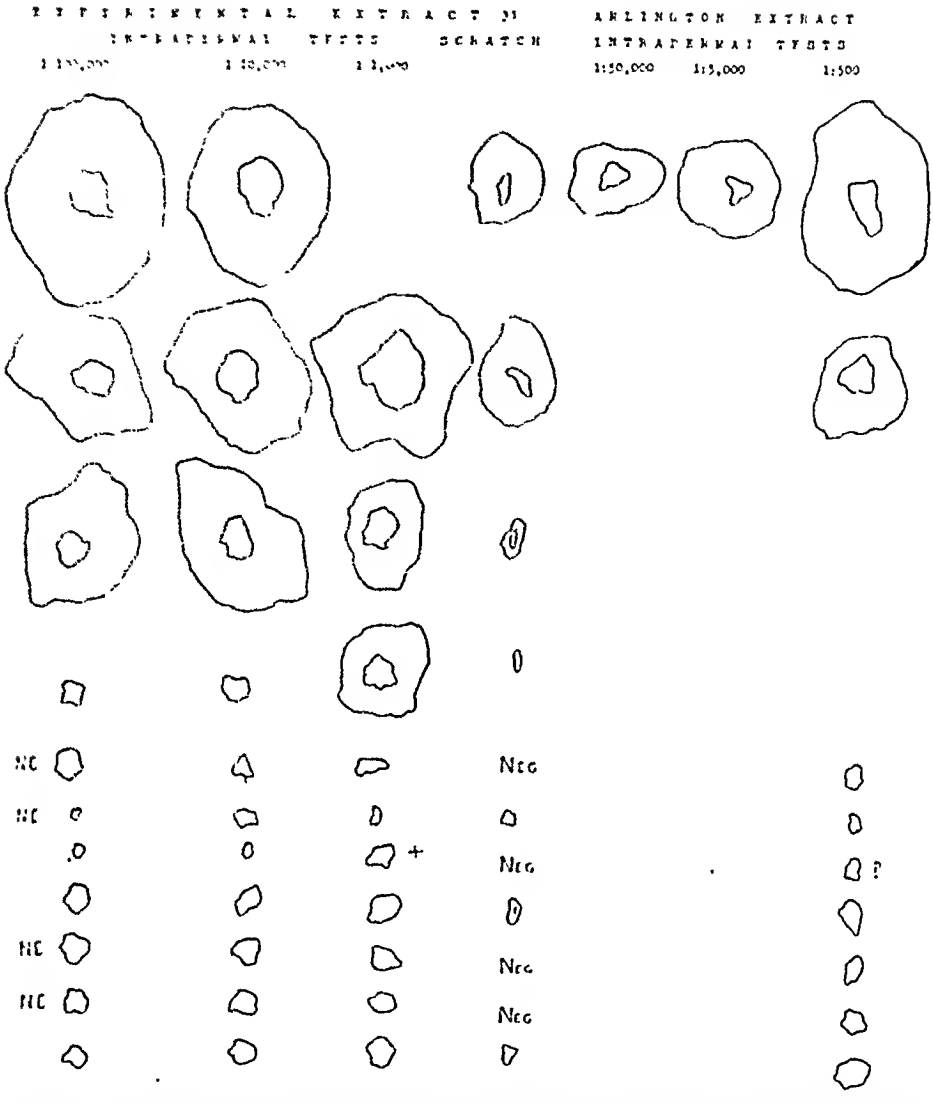

Fig. 1. Tracings of reactions to extract 33 and to a commercial extract (Arlington) in five patients sensitive to Alternaria, two sensitive to other substances, and four normal persons.
N.C. = normal control. (S.E.)

present in all the experimental extracts, indicating that no clear-cut separation into reactive and non-reactive fractions was obtained. This was not entirely unexpected, since the various precipitates had been obtained empirically with varying acetone concentrations, and might not necessarily represent *distinct* fractions. Generally, however, those fractions precipitated with an acetone concentration of 75 per cent or less seem more reactive than those obtained with greater amounts of acetone, suggesting that the allergen is almost although not completely precipitated by 75 per cent acetone. On the other hand, there is no clear difference in skin reactivity determined by the appearance of the precipitate unless the results with extracts 28 and

TABLE II. COMPARATIVE TESTING ALTERNARIA EXTRACT 33

INTRADERMAL TESTS								SCRATCH PUNCH		
1/100,000		1/10,000		1/1,000		1/100		1/50		
Extract 33	Regular Method Extract	Extract 33	Regular Method Extract	Extract 33	Regular Method Extract	Regular Method Extract	Extract 33	Regular Method Extract		
+	++	++	+	++++	++++		+	++		H.E.P.
++++	+	++++	++	++++	++++	++++	++	+		H.E.P.
++	+	++++	++		+++		+++	+		H.E.P.
+		++++		+++			+	+		H.E.P.
+				+++		++++	+	+		H.E.P.
+		+			"x"		++	+		H.E.P.
+		++		++++		+++		+		H.E.P.
++++	—	++++	+		++					H.E.P.
++	—	++++	+		+++					H.E.P.
+		++++			+	+++				H.E.P.
++++		++++			+++					H.E.P.
—		+	—	+	+	++++				H.E.P.
+		+++		++++	++++					H.E.P.
+++		++		++++					—	H.E.P.
+	—	++++	—	++++	++++	++++		++	+	H.E.P.
—		++		++++	+++	++++		+++	—	H.E.P.
—		+++		+++	—			—	+	L.D.H.
—		—		++	—			—	—	L.D.H.
++++		++++		+++++	++++			—	++	L.D.H.
								++++	+	L.D.H.
—		—		++	—			—	—	
Patients Tested 10 Reacted 14 74%		Patients Tested 19 Reacted 17 89%		Patients Tested 15 Reacted 15 100%				Patients Tested 14 Reacted 10 71%		

"x" Test caused asthma

TABLE III. TESTS ON ALTERNARIA-SENSITIVE PATIENTS

INTRADERMAL TESTS 1/1,000		SCRATCH TESTS	
Hollister-Stier	33	Hollister-Stier	33
++	+++"x"	++	++
++	++	++	+++
++	+++	+++	++++
+++	++++	++	+++
++	+++	++	+++
++	+++	+	+++
++	+++	+++	++++"x"
++	++	++	+++
++	+++	+++	+++
++	++	+++	+++
+	++"x"	+++	++++
		++	+++
		++	++
		+	++

"x"—Sensitive only to Alternaria

TESTS ON ALLERGIC PATIENTS SENSITIVE TO OTHER FACTORS THAN ALTERNARIA

Patients Tested	6	6	19	19
Positive Reactions	0	0	0	0
Negative Reactions	6	6	19	19

K.D.F.

30, both of which were derived from flocculent precipitates, may suggest that re-precipitation concentrates the antigen (compare extracts 29 and 31 both of which were made from oily precipitates). The results of the intradermal tests with 1/100 dilution cannot be accepted for studying any differences in the extract, but they do reveal the presence of antigen even in those extracts which did not possess a high reaction titre.

PREPARATION OF EXPERIMENTAL EXTRACT 33

Following the studies outlined above, which revealed the presence of antigen in precipitates obtained by all concentrations of acetone from 50 to 93 per cent by volume, we proceeded to prepare experimental extract 33 to include *all* fractions precipitable by an excess of the reagent. Accordingly, a general technique of adding nine volumes of cold acetone to a preliminary aqueous extract with rapid stirring was followed. The exact technique still in process of definition will be published in the near future. The mixture was placed in the cold (−20° C) for twenty-four hours, after which all the precipitate was collected by centrifugation. After removal of the acetone, the precipitate was dissolved in water, lyophilized, and dissolved in Hollister-Stier solution in the ratio of 1/50. This extract was distributed to various members of our group for skin testing on Alternaria-sensitive patients.

SKIN TESTING WITH EXTRACT 33

In Table II are shown the results of intradermal and punch (scratch) tests on Alternaria-sensitive patients with extract 33, as well as with our "regular method" extract. One of us (K.D.F.) tested a series of allergic patients both sensitive and non-sensitive to Alternaria with extract 33 and with a commercial product (Hollister-Stier) (Table III). Figure 1 shows the tracings of reactions to extract 33 and to another commercial extract (Arlington) in five patients sensitive to Alternaria, two sensitive to other substances, and four normal persons.

Most of these tests suggest the superiority of extract 33; especially in Table II and Fig. 1 do higher dilutions of extract 33 produce equal or greater reactions than the other extracts under comparison. Unfortunately, it was impossible to include extract 33 in the series dealing with extracts 13 to 32 discussed earlier in this paper. However, the percentage of positive reactions for each dilution of extract 33 is slightly greater than for the corresponding dilutions of extract 13, the only other extract approaching 33 in reactivity. Furthermore, since in dilution of 1/1,000 extract 33 reacted on 100 per cent of Alternaria-sensitive patients, whereas extract 13 reacted in only 89 per cent in similar dilution, and in 95 per cent of cases in a tenfold (1/100) concentration, this slight difference has added significance.

CONCLUSION

Variations in acetone precipitation of a preliminary aqueous extract of Alternaria are presented. Skin tests on Alternaria-sensitive patients suggest that precipitation with nine volumes of acetone gives an extract of higher potency than any experimental extract previously studied by us.

REFERENCES

1. Prince, Homer E. and Morrow, Marie B.: Mold fungi in the etiology of respiratory allergic diseases. III. Immunological studies with mold extracts. 1. Preparation of experimental extracts. Ann. Allergy, 2:483, 1944.
2. Prince, Homer E.; Tatge, Edward George; and Morrow, Marie B.: Mold fungi in the etiology of respiratory allergic diseases. V. Further studies with mold extracts. Ann. Allergy, 5:434, 1947.

THE USE OF ANTIHISTAMINIC DRUGS IN HUMAN TUBERCULOSIS

A Preliminary Report

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PRIMARY tuberculosis is characterized, in the great majority of cases, by its relative benignity and absence of tissue destruction. These characteristics are reversed in the reinfection or secondary phase. This reversal is dependent upon hypersensitivity to an antigen which is developed during the primary phase and maintained as long as tubercle bacilli remain within the body. Upon reinfection or spread of the bacilli from a primary site, there occurs an inflammatory reaction, which is characterized by exudation and may be followed by caseation necrosis.[7] If this acute inflammation could be prevented, a significant advance in tuberculosis therapy would be achieved. It seemed possible that antihistaminic drugs might protect sensitized cells from injury and thus alter the course of the disease. This preliminary report is concerned with the effects of antihistaminic drugs upon human tuberculosis.

The drugs* employed, as the salts, were diphenhydramine (Benadryl), tripelennamine (Pyribenzamine), phenindamine (Thephorin), and thonzylamine (Neohetramine). Patients were started on 50 mg. of the antihistamine three times daily. The dose was increased to 300-400 mg. per day, as tolerated. The highest daily dose given any patient was 500 mg., and the longest period of administration was seven months. Benadryl and Pyribenzamine were first used, but they were not well tolerated in large doses. When it was necessary to discontinue a drug because of side effects, patients were transferred to Neohetramine because it is reported to be less toxic than other available antihistaminics.[1-6,8-10] It is evident that the least toxic drug should always be used, but this is especially true in an already toxic patient, particularly one fighting the insult of an acute exudative or pneumonic lesion. No significant changes were observed in the urine, erythrocyte sedimentation rate or differential leukocyte count. A moderate increase in pulse rate was almost always noted after institution of therapy.

Patients presenting pulmonary and non-pulmonary manifestations of tuberculosis were studied. Among the patients presenting pulmonary manifestations of the disease were cases of tuberculous pneumonia, acute exudative cases, mixed exudative and fibrotic cases, and advanced chronic fibrotic cases. A total of thirty patients is presented in this preliminary report. The type of disease and the results obtained are presented in Table

---

Presented at the fifth annual session, the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*We are indebted to Wyeth, Incorporated, for the supply of Neohetramine, manufactured by the Nepera Chemical Co., Inc., and to Hoffman-LaRoche for the supply of Thephorin.

TABLE I.

RESULTS OF ANTIHISTAMINE THERAPY IN PULMONARY TUBERCULOSIS*

Type of Lesion	No. Cases	Cough			Sputum			Weight			"Well-Being"			X-Ray Lesions (Densities)			Chest Pain			Appetite			Temperature			Mantoux Reaction	
		Increase	Decrease**	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Conversion to Negative	Not Converted
Exudative and T.B. Pneumonia (Acute)	6 2 — 8	0	7	1	0	7	1	6	2	0	7	0	1	0	7	1	0	2	4	5	0	3	1	3	4	6	2
Mixed—(Productive and Exudative)	14	1	9	4	1	9	4	8	2	4	10	1	3	1	4	9	0	4	10	6	0	8	0	2	12	11	3
Productive (Fibrosing)	8	2	2	4	2	2	4	1	4	3	1	1	6	1	0	7	0	0	8	0	2	6	0	0	8	7	1
Totals	30	3	18	9	3	18	9	15	8	7	18	2	10	2	11	17	0	6	22	11	2	17	1	5	24	24	6

*All patients received at least 10 weeks of drug treatment.

**In most instances thinning and almost complete absence of sputum was observed.

I. Physical findings have been omitted, so frequently, they do not parallel the roentgenological findings. Four case abstracts illustrate the effect of antihistaminic drugs.

Case 1.—M.R., A 24-year-old colored woman, was admitted October 29, 1947, following a four-month history of weight loss, anorexia and one episode of hemoptysis. On admission her only symptoms were a slight cough and a negligible amount of sputum. The x-rays revealed scattered infiltrations irregularly throughout both lung fields without evidence of excavation. Sputum was negative on the first two examinations but positive on the third. The blood showed: RBC, 4,850,000 Hb. 12 Gm. (79 per cent), WBC 6,200, with a normal differential; and sedimentation rate 14 mm. in sixty minutes. Urine was normal by routine examination. This patient was placed on bed rest. Several attempts at artificial pneumothorax found the pleural space obliterated.

She was apparently running a satisfactory course (Fig. 1) with only occasionally positive sputum, when six months following admission she suddenly became febrile (temperature 104° F.), had a sudden drop in weight, loss of appetite and severe prostration. She was placed in a quiet room. As she was too ill to transport to the X-Ray Department, a portable film was taken at the bedside. This showed the left side to be obliterated by a dense homogeneous shadow (Fig. 2). Four days following this acute episode, April 24, 1948, she was placed on Pyribenzamine. The initial dose was 200 mg. daily. When the dose was elevated, she became dizzy and nauseated, so the initial dose was maintained. The Mantoux test† at the onset of medication was plus 2. She had lost nine pounds in the one week prior to medication. After one week of antihistaminics, her temperature was normal. She no longer lost weight. Her malaise was quickly disappearing. By the third week she had improved to the point where she was placed back in the ward. Her appetite had returned. Her Mantoux test was still plus 2. She had gained two pounds. Her cough had lessened, and her sputum had thinned considerably, but had not diminished

†P.P.D. first strength was used throughout this series except for one patient who required the second strength.

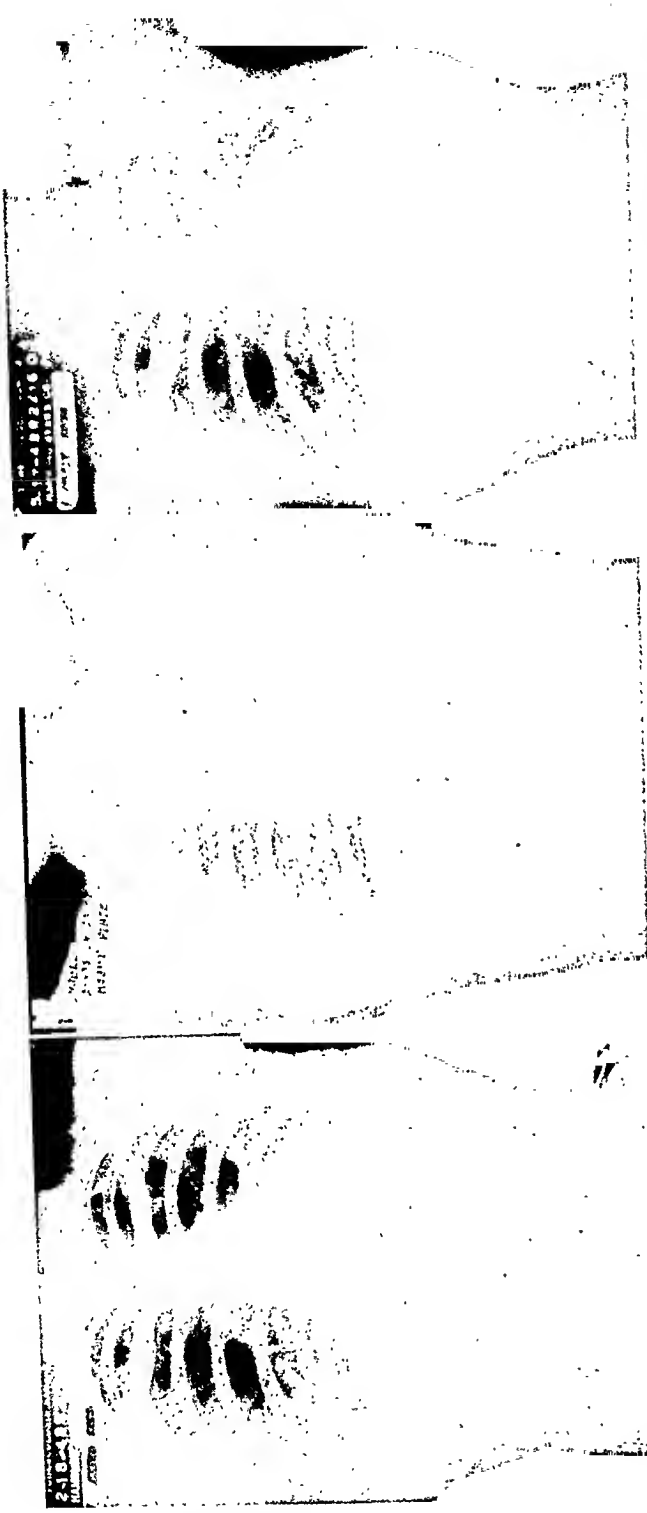

Fig. 1. Case 1. M.R., black, female, aged twenty-four. Roentgenogram taken February 18, 1948 reveals moderately advanced tuberculosis in both lung fields.

Fig. 2. Case 1. Bedside roentgenogram taken April 22, 1948, twenty-four hours following the acute onset of a left tuberculous pneumonia, accompanied by high fever (101 F.), chest pain and marked prostration. Antihistamines were started after this view was taken.

Fig. 3. Case 1. Roentgenogram taken May 17, 1948, after twenty-one days on antihistamines. Temperature was normal after the first week of therapy. By the time this view was taken the patient was well enough to be removed from the quiet room and was placed back on the ward. Note marked clearing of the entire left side. No definite evidence of excavation or fluid is seen.

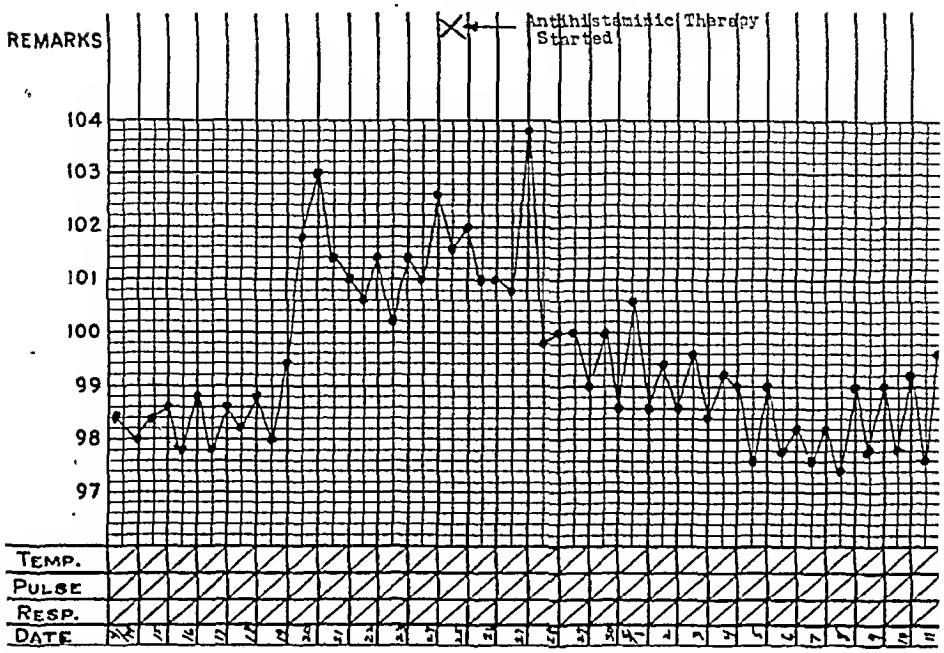

Chart 1. M.R. The temperature elevation in this case reflects the sudden onset of the acute tuberculous involvement. It is well to note that such an elevation does not always accompany an acute dissemination of the infection and similarly that a normal temperature range can exist in the presence of an acute progression of the disease process. See Chart 3. (April 14 to May 11, 1949.)

in quantity. By the fifth week her Mantoux test had diminished to plus 1, and by the seventh week was negative. The Mantoux findings did not remain negative, however, but became intermittently positive (never more than plus 1). X-Ray revealed considerable clearing of the left side by one month (Fig. 3). The patient's vigor had returned considerably. She was kept on 200 mg. daily of Pyribenzamine for thirteen weeks. It was discontinued because of increasing nausea and palpitation. During this period she had regained seven pounds and toward the end of it had no cough whatsoever. Her sputum, likewise, had disappeared and what she could force up was negative for tubercle bacilli.

This patient received no antihistamine for the next eighteen weeks. Her cough gradually increased, and she began to produce a greenish-yellow tenaceous sputum. The Gaffky count was plus 2 on two occasions when she was not taking antihistamine therapy. She lost two pounds during the first month. These were regained after a few weeks. She ran irregular bouts of elevated temperature, reaching 101.4° F. and tachycardia. Roentgenograms revealed an extension of the lesions in the right upper lung field. There were no significant urine or blood changes except for marked increase in the sedimentation rate (from 14 to 27 mm. Cutler method). Antihistamines were again administered. Pyribenzamine caused restlessness and insomnia as well as nausea, and it was replaced by Neohetramine, 150 mg. daily. This dose was gradually increased until a maintenance dose of 350 mg. daily was obtained. The patient, to date, has been on this second course of drug for seven weeks. Her cough again has markedly decreased, and she now produces only one-fourth the quantity of sputum that was expectorated at the onset of this second course. The sputum has thinned considerably but remains positive for tubercle bacilli continuously and contains occasional blood streaks. The Mantoux test is constantly positive (plus 1). Roentgenogram reveals new lesions which appeared in

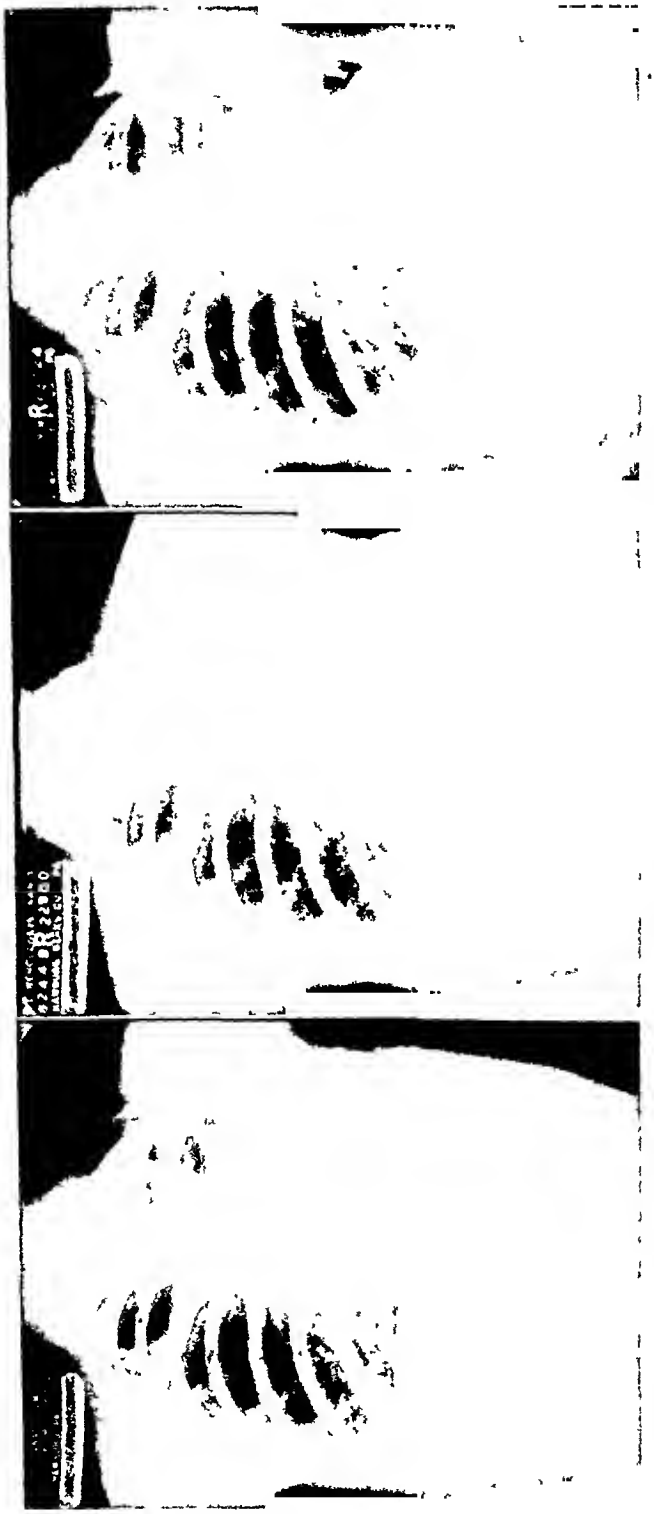

Fig. 4. Case 2. V.J.M. Admission roentgenogram taken July 20, 1948. This 26-year old white woman had a six-month course of streptomycin, one to three grams daily, one year prior to admission, without beneficial results. A large cavity can be seen in the left lung just above the dense area of tuberculous pneumonia

Fig. 5. Case 2. Roentgenogram taken after one month on antistreptomycin. There is considerable clearing of the left lower lobe as well as some of the exudative reaction in the upper lobe on this same side.

Fig. 6. Case 2. Roentgenogram taken five months after the onset of streptomycin therapy. The left lung contracts to clear, the right lung remains clear.

the interval between the first and second courses of antihistamine drug. The sedimentation rate remains 27 mm. in thirty minutes. There have been no significant changes in the blood picture or urine analysis of this patient.

Case 2.—V.J.M., A 26-year-old white woman, was admitted June 2, 1948, with a history of pulmonary tuberculosis of one and one-half years. One year prior to admission to this institution, she had received 1 to 3 grams of streptomycin daily for six months without evidence of improvement. She had received no therapy other than bed rest for six months preceding the present admission. Laboratory findings were as follows: Sedimentation rate 20 mm. in sixty minutes; red blood cells 4,100,000; hemoglobin 12.5 Gm. (82 per cent); white blood cells 10,400; differential normal; sputum Gaffky count, plus 4, plus 6, and plus 4; vital capacity 2 liters; weight 112 pounds. Roentgenogram of the chest showed a large cavity in the left upper lung and pneumonic consolidation in the left lower lobe (Fig. 4).

The temperature following admission ran between 98.2° and 103° F. The patient appeared ill. Because of the exudative nature of her lesion and the obvious toxicity, she was considered a candidate for antihistamine therapy (Chart 2).

Pyribenzamine was given daily in doses of 150 mg., but because of undesirable side effects she was placed on Neohetramine. Doses up to 350 mg. daily were maintained without untoward effects. Her general feeling of well-being was considerably improved. She was obviously less toxic. Her appetite, however, had not yet returned. She was losing weight slowly. The roentgenogram showed evidence of parenchymal clearing (Fig. 5). After five months on Neohetramine therapy, she had improved considerably in all ways except that her appetite was still very poor and there had been a gradual loss of weight to 102 pounds. Her sputum remained positive. The Mantoux skin test had changed from a plus 2 at the onset of medication, to negative in eight weeks. Bi-monthly Mantoux tests have remained negative to date, with the exception of two faint reactions. Roentgenograms of the chest showed further clearing of the left lung (Fig. 6).

To date there have been no significant blood or urinary changes. It is a notable fact that the disease continued to progress despite prolonged treatment with streptomycin. Progression was halted, and the exudative lesions began to clear after Neohetramine was given.

Case 3.—V.L., A 20-year-old Mexican woman, was admitted January 21, 1948, with the diagnosis of bilateral pulmonary tuberculosis with cavitation. At no time prior to admission had this patient complained of symptoms referable to the chest or to the disease. A survey roentgenogram discovered these lesions. On admission, the sputum Gaffky count was plus 6, plus 7, plus 4. There were no significant urinary findings. The blood showed: red blood cells 4,920,000; hemoglobin 11 Gm. (73 per cent), white blood cells 15,300, with a normal differential count; sedimentation rate 28 mm. in sixty minutes. Vital capacity was 1.5 liters. Almost immediately following admission, she developed a cough which produced enough thick yellowish sputum to cover the bottom of her sputum box. Roentgenograms of the lungs on admission revealed lesions which were classified as far advanced, exudative in type, and bilaterally apical in location. Several small cavities were present in the apices of both lungs (Fig. 7). The patient was placed on bed rest. In a month's time, it became obvious that the course was of a down-grade nature. Her cough increased, sputum increased in quantity and continued positive for tubercle bacilli. She became obviously toxic with symptoms of pain in the chest, loss of weight, sweats, and an irregular, low grade fever ranging between 97° and 100° F.

On April 19, 1948, administration of 150 mg. of Pyribenzamine daily was begun. In one week, the dose was increased to 200 mg. daily. At subsequent weekly intervals, the dose was increased until a dosage of 400 mg. was taken daily. The Mantoux

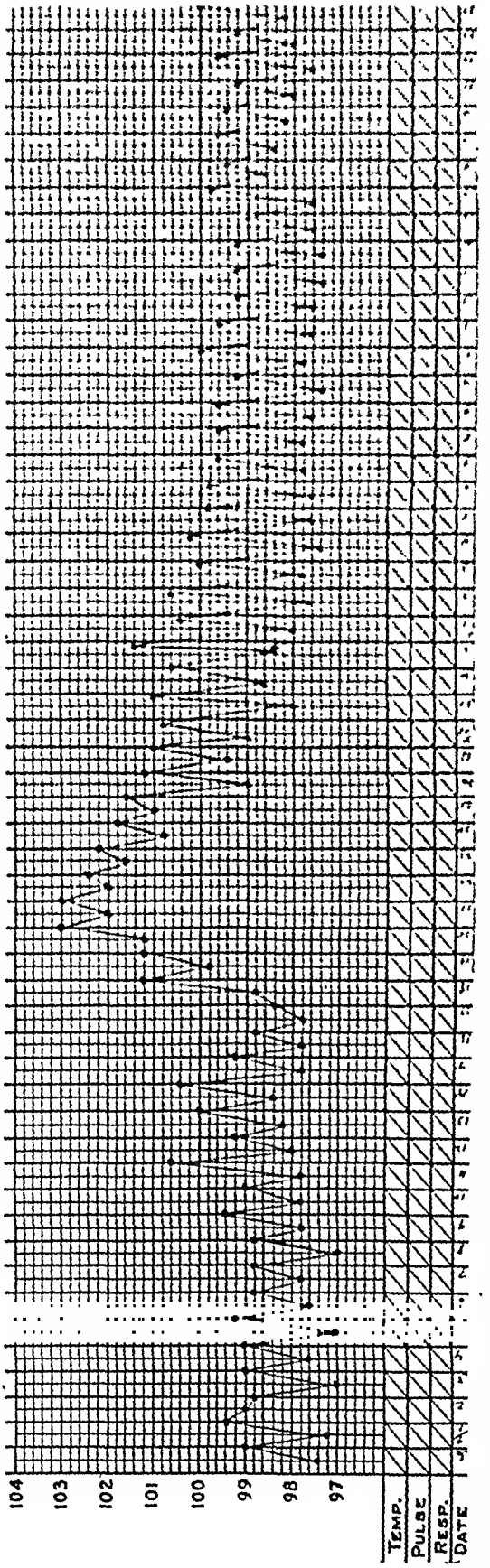

Chart 2. Temperature record of V.J.M. from May 30 to July 21, 1917, illustrating a type of febrile reaction similar to that seen in Chart 1. A [illegible] decrease was noted after the administration of antihistaminic therapy following the sudden temperature rise seen in the center of the chart.

Fig. 7. Case 3. Admission film of V.L., a Mexican woman, aged twenty. Multiple excavations are seen in the right and left upper lobes. Clinical course was on the down-grade with weight loss and obvious toxicity.

Fig. 8. Case 3. After one month on antihistamines. Exudative phase of lesions is greatly diminished. Excavations bilaterally conmany having completely course reversed. Weight gain obvious on the film.

skin test prior to the initial dose was 3 plus. Two weeks following the onset of medication, the Mantoux test was 2 plus. Two weeks later it was still 2 plus. However, during the sixth week, the test was negative, and with the exeeption of one faint reaetion, it remained negative for ten weeks (five tests). During the sixteen weeks of antihistaminic therapy, symptoms of toxicity disappeared rapidly. The patient ate well and she gained thirteen pounds during this period. Her temperature beeame normal in two weeks and was never elevated above 99° F. A Roentgenogram (Fig. 8), taken one month following the administration of the first dose of antihistamine drug, revealed marked elearing of the exudative lesions in both lung fields, and the eavity in the right upper lung field had almost disappeared. No urinary or blood changes were noted. Two repeat sedimentation rates were both 26 mm. in sixty minutes. The sputum Gaffky eount dropped to plus 3, then plus 2. Her general feeling of well-being increased remarkably. Cough and sputum were almost negligible. After sixteen weeks, medication was diseontinued. During the period of administration of the drug no side effects presented themselves which could be related to the antihistamine.

One week following the discontinuanee of the drug, the patient began to cough more frequently, and her sputum began to increase; the Gaffky count became plus 4. The Mantoux reaction returned positive (plus 2) in ten days. For the first time in her life, she experieneed amenorrhea. The pulse became elevated with a rate between 100 and 108 beats per minute. Her appetite began to disappear and she lost seven pounds in weight. The Mantoux test remained persistently positive. The patient's eourse was obviously down-hill. The x-ray revealed a spread of the lesions (Fig. 9). After thirteen weeks without antihistamines, she was again plaeed on Pyribenzamine, 150 mg. daily. The dose was gradually increased, as before, until a total of 350 mg. were being taken daily. She began to complain of dizziness after five weeks on this schedule. Pyribenzamine was diseontinued, and she was immediately placed on Thephorin therapy. She reeeived a daily dose of 200 mg. of this drug. Two weeks following the reinstitution of antihistamine medieation her cough was praetically

Fig. 9. Case 3. Roentgenogram taken two months following the discontinuance of antihistamine therapy. Considerable spread of the lesions can be seen in the mid-lung field on the left. This was accompanied by amenorrhea and a return of the symptoms of toxicity.

Fig. 10. Case 3. Roentgenogram taken after one month on the second course of antihistamines. The spread seen in the left lung field can be seen to have cleared. Amenorrhea ceased. Clinical course again reversed.

absent and only slight in the morning. At this time, she produced a small amount of sputum which had turned from a thick, yellowish to a thin, whitish appearance. She menstruated for the first time in nearly four months. The Mantoux test was plus 1. Her appetite increased and she gained two pounds during the first two weeks. The lesions again began to decrease (Fig. 10). At the present time this patient is continuing her second course of antihistamines. During the entire course thus far no significant changes have been noted in the routine blood and urine studies.

Among the extrapulmonary group was one case each of laryngeal and glandular tuberculosis, and one case of erythema nodosum. The first patient presented a laryngeal tuberculosis (Type IV, Grade IV), causing severe pain and hoarseness for a period of six months. This patient was treated with dramatic symptomatic relief which persisted until the patient died as a result of a massive pulmonary hemorrhage. A second patient presented an axillary gland involvement as a complication in a case of a stabilized and apparently arrested pulmonary tuberculosis.

Case 4.—K.W., aged twenty-six, white, female, housewife, giving no clinical history referable to the respiratory system was first seen at another hospital complaining of a mass in the left axilla. This mass was removed surgically, examined microscopically, and found to be tuberculous. A roentgenogram of the chest was then made, and a minimal pulmonary tuberculosis was discovered. She was soon thereafter admitted to the Hamburg Sanatorium.

On admission here the clinical history and physical examination were essentially negative or non-contributory except for a well-healed axillary scar.

The laboratory findings were as follows: Hemoglobin 91 per cent; red blood cells 5,660,000; white blood cells 11,100; polynuclear neutrophiles 48 per cent; small

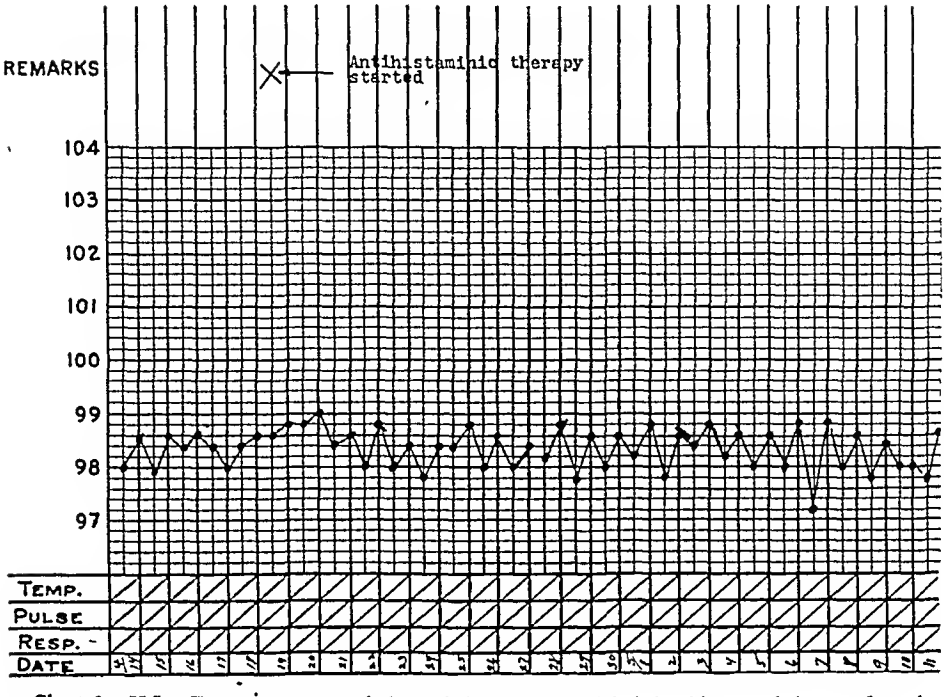

Chart 3. V.L. Temperature record (recorded three times daily) in this case fails to reflect the acute pulmonary episode seen on the roentgenogram.

lymphocytes 46 per cent, mononuclear 3 per cent, eosinophiles 3 per cent, sedimentation rate 21 mm. in sixty minutes (Cutler method): Sputum was negative for acid-fast bacilli on all examinations, including gastric washings and culture. Basal metabolism rate –9; Wassermann negative; urine normal. X-Ray revealed a minimal lesion in the left pulmonary apex. Temperature, pulse, respiration always remained within normal limits.

Two months after admission an axillary mass suddenly developed near the site of the previous excision. This mass enlarged to the size of an average fist, was tender and obviously inflammatory. It was felt that there had been a recrudescence of the axillary glandular tuberculosis.

The patient was placed on 50 mg. of Pyribenzamine four times daily. This dose was shortly increased to a total of 300 mg. daily, and she was maintained on this schedule. In one week's time the pain in the region had been reduced. After two weeks, there was an obvious decrease in the size of the mass. Pain and tenderness was greatly diminished. By four weeks, the glandular mass had been reduced to the size of a walnut and tenderness was only slight. By the ninth week, the mass was reduced to the size of an almond, and tenderness could only be elicited by pressure. Thereafter, no further change was noted. The Pyribenzamine therapy, 300 mg. daily, was continued for a total of four months. After the ninth week, there was no further change noted in the axilla. The small pulmonary lesion had remained stable throughout the course. Prior to instituting antihistaminic therapy, the Mantoux reaction was plus 2. By the third week it was plus 1 and on the fifth week it was negative and remained so thereafter throughout the remainder of the course of therapy. The patient was discharged August 10, 1948, after seventeen weeks of antihistaminic therapy. No change in the patient's status has been reported since discharge.

Case 5.—G.H., aged twenty-seven, white, female, meat handler, was admitted nine months following the onset of symptoms which had their onset in September, 1947, when she developed a productive cough and debility, accompanied by a weight loss (15 pounds), anorexia, fatigue and night sweats. The physical examination on admission was essentially normal except for evidence of recent loss of weight and signs characteristic of a bilateral pulmonary tuberculosis with cavities in both lungs. Her temperature, pulse and respiration were normal except for an increased respiratory rate up to 28 per minute.

The laboratory findings were as follows: Red blood cells 4,920,000; hemoglobin 88 per cent; white blood cells 17,100; polynuclear neutrophiles 67 per cent; lymphocytes 33 per cent; urine negative; Wassermann negative. Fecal smear—acid-fast bacilli found. Sputum was positive for acid-fast bacilli. Gaffky count was 4, –, 6. Sedimentation rate was 26 mm. in sixty minutes (Cutler method). X-rays revealed bilateral pulmonary tuberculosis with cavitation with greatest degree of involvement in left lung.

Right artificial pneumothorax was successfully instituted (left unsuccessful) and has been maintained without complication. In spite of therapeutic measures, including streptomycin (1 gm. daily, i.e. ½ gm. morning and afternoon for fifty-eight days directed specifically against the tuberculous enteritis), the patient's course continually progressed down-hill with weight loss, irregular temperature elevations to 101—102° F. and evidence of toxicity and tuberculous enteritis.

Six months following admission, she presented an erythema nodosum involving both pretibial areas. Antihistaminic treatment, Benadryl 100 mg. daily for five days, was followed by regression of the lesions within five days, leaving the characteristic residual pigmented areas. The medication was then discontinued. Two weeks following cessation of medication, new nodules appeared and the original nodules reappeared. Antihistaminic therapy, Pyribenzamine 150 mg. daily, was resumed and continued for one month, although all lesions regressed within three days and have not since reappeared.

DISCUSSION

In these thirty cases the clinical response was graded roentgenographically and by temperature changes, character and quantity of sputum; increase in weight, appetite, and feeling of well-being were noted. As seen in Table I, the greatest improvement occurred in patients with tuberculous pneumonia and other acute exudative lesions, which, in our opinion, are a result of hypersensitivity.[7] It is significant that, as the lesions progress in chronicity, the antihistamine drugs become less effective.

Mantoux tests were performed on all patients. Purified Protein Derivative Tuberculin, USP, was used prior to, during, and after administration of the drug. In most instances, a gradual diminution in the intensity of the reactions occurred while antihistaminic drugs were taken. The conversion was not always complete, however, and many individuals occasionally showed a slight positive reaction. The reaction became positive within about four to six weeks after administration of the antihistaminic drug was stopped. Although skin sensitivity is not necessarily a measure of hypersensitivity existing in other tissues, it would appear from our results that clinical improvement roughly parallels suppression of the Mantoux reaction.

Three of the patients who showed striking improvement coincident with

antihistaminic therapy were taken off this medication. Within two to eight weeks, symptoms and signs of the disease recurred and retrogression of the pulmonary lesions were demonstrable by x-rays. Reinstitution of therapy was again followed by striking improvement in all three patients. In these patients, the clinical improvement accompanying the administration of the antihistamines strongly points to the therapeutic effectiveness of these drugs even though improvement lasted only through the administration. The combined administration of antihistaminic drugs to suppress the allergic components of the disease, and streptomycin to suppress the growth of the bacillus, may be very effective treatment. Such combined therapy is under active investigation.

The authors realize that thirty cases are too few to evaluate fully the effectiveness of the antihistamines in human tuberculosis, but feel that such a preliminary report will make possible wider investigation than can be accomplished in any one single clinic.

SUMMARY

The antihistamine drugs have been used with encouraging results in the treatment of human tuberculosis. The best results were obtained in the acute exudative type of tuberculosis. The Mantoux reaction was diminished during antihistamine therapy. Additional clinical investigation is in progress.

The authors acknowledge their indebtedness to John E. Gregory, M.D., for his kind help in these studies.

BIBLIOGRAPHY

1. Alexander, H. L.: Private communication, 1948.
2. Arbesman, C. E.: J. Allergy, 19:178, 1948.
3. Black, J. H.: Private communication, 1948.
4. Criep, L. H., and Aaron, T. H.: J. Allergy, 19:215, 1948.
5. Feinberg, S. M.: Private communication, 1948.
6. Friedlaender, S., and Friedlaender, A. S.: J. Lab. & Clin. Med., 33:365, 1948.
7. Rich, A. R.: The Pathogenesis of Tuberculosis. Springfield, Illinois: Charles C. Thomas, 1944.
8. Roberts, E. F.: Indust. Med., 17:263, 1948.
9. Waldbott, G. L., and Borden, R.: Ann. Allergy, 6:305, 1948.
10. Waldbott, G. L., and Young, M. I.: J. Allergy, 19:313, 1948.

IMPORTANT NOTICE!

All members of the College who desire to submit a paper either to be read or to be presented BY TITLE at the Sixth Annual Session to be held at the Jefferson Hotel, St. Louis, January 15, 16, 17, and 18, 1950, are requested to send the manuscript, together with an abstract, to the Chairman of the Program Committee, Dr. Sim Hulsey, 701 Fifth Avenue, Fort Worth, Texas, by September 1, 1949.

NEOHETRAMINE IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS

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IN the course of our studies of Neohetramine,* it occurred to us that this drug might be beneficial in the treatment of tuberculosis by reducing the allergic reaction of the host to the spread of the tubercle bacillus in the body. This, in effect, might be considered a nonspecific method of desensitization. Specific desensitization by means of graded tuberculin injections, while beneficial in some forms of tuberculosis, is not without danger, and may be used only with great caution.[11] Since Neohetramine has been widely used in large numbers of patients with a minimal incidence of unimportant side effects,[1,4,5,10] it appeared that this drug might afford the benefits of specific desensitization without its danger.

The present communication is a preliminary account of our studies of the effect of Neohetramine on guinea pig tuberculosis.

EXPERIMENTAL

Two consecutive experiments, in which identical methods were used, are reported herein. In each experiment, twenty young tuberculin-negative guinea pigs (400-500 gm.) were infected subcutaneously in the groin with 0.1 mg. of virulent human-type tubercle bacilli (H37RV). All reacted to 1 mg. of Old Tuberculin (Mantoux method) ten days after infection, at which time they were divided into two groups of ten. Each animal in the first group was given 6 mg. of Neohetramine subcutaneously, twice daily, at 9:00 a.m. and 5:00 p.m. The other group was used as untreated controls. All the guinea pigs were weighed and tested with 1 mg. of Old Tuberculin (Mantoux method) at frequent intervals. The only deaths that occurred before the end of the experiment, in which tuberculosis was a major factor, were in the control groups, each of which lost two guinea pigs at times varying from sixty-nine to eighty-four days after infection. Animals were autopsied as soon as possible after death, and all survivors were sacrificed three months after the beginning of treatment. The amount of disease in lungs, liver, spleen, and lymphatic system was estimated. Extensive generalized involvement of an organ is denoted by 4-plus, while minimal involvement, consisting usually of a few discrete lesions, is denoted by 1-plus. Sections of the organs were stained with hematoxylin-eosin and with the Ziehl-Neelsen stain, and the lesions were studied for type of disease and content of acid-fast bacilli.

RESULTS

At no time did the treated guinea pigs show any change in reaction to 1 mg. of Old Tuberculin intracutaneously. The failure may be due to in-

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From the Research Laboratories of Nepera Chemical Co., Inc., Yonkers, N. Y.

TABLE I. AVERAGE GROSS TUBERCULOSIS IN CONTROL AND IN NEOHETRAMINE-TREATED GUINEA PIGS

Exp.	Group	No. g. pigs	Lungs	Liver	Spleen	Glands	Summary
1.	Controls	10	1.2	1.3	2.0	2.6	7.1
	Neohetramine	10	0.6	0.4	0.9	1.5	3.4
2.	Controls	9	1.0	1.4	1.5	2.7	6.6
	Neohetramine	9	0.2	0.3	0.9	1.1	2.5

sufficient concentrations of the drug in the skin.[2,3,6,7] They tolerated the two daily subcutaneous injections of Neohetramine without evidence of local toxicity. Average weight curves for the four groups of animals showed no consistent trend. This weight response, together with the absence of local toxicity, indicates that Neohetramine was well tolerated. Gross findings at autopsy showed that the treated animals had about half the disease found in the controls (Table I).

Microscopic examination of the tissues showed that the H37RV organism, at the infecting dose employed, caused in the control guinea pigs a somewhat slowly progressive disease with moderate fibrosis and caseation. There were small numbers of acid-fast bacilli in the lesions, the cells of which were principally monocytes and epithelioid cells. In the treated animals, however, the disease was decidedly more chronic in character, the tubercles showing more fibrosis, while lymphocytes were prominent among the cells of the lesions. Acid-fast bacilli were rare and often impossible to find in the treated animals. This difference was especially marked in the second experiment.

DISCUSSION

The reasons for the beneficial effects of Neohetramine are not known. A direct antimycobacterial action *in vivo* is improbable because in experiments completed at this time Neohetramine has exhibited no effect on the tubercle bacillus *in vitro*.[9] It is possible, though unlikely, that some metabolic product of Neohetramine may be active. We are inclined to believe that Neohetramine is effective in experimental tuberculosis because of its ability to suppress hypersensitivity reactions. Because of this property, the violent reaction of sensitized tissue to the introduction or the spread of tubercle bacilli may be lessened. If so, tissue and capillary damage are reduced, and the toxemia and pyrexia may be diminished. Under such circumstances, it is conceivable that the natural defenses of the host may be better able to resist the invading microorganisms.

Neohetramine seems best suited for the treatment of tuberculosis which is predominantly exudative in type. Since this is the type of disease in which Streptomycin is most useful, combined therapy should be considered, and for that reason, the effect of both Neohetramine and Streptomycin on guinea pig tuberculosis is under laboratory investigation. If the beneficial effects of Neohetramine in experimental tuberculosis are due to its effect on the hypersensitive state of the animal, the clinical trial of Neohetramine

(Continued on Page 376)

A CLINICAL EVALUATION OF NEOHETRAMINE IN ALLERGIC DISEASES

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THE theory is generally accepted that as a result of an antigen-antibody reaction there is a liberation of histamine, or histamine-like substance, thus causing allergic symptoms in the shock tissues. It is consequently logical to assume that if the histamine liberated could be neutralized or antagonized by a drug that would attach itself to the histamine cell receptors, thus blocking the attachment of released histamine, patients would become symptom-free, or symptoms would be held to a minimum.

Certain phenolic ethers were demonstrated by Fourneau and Bovet[1] in 1933 to have such antihistamine, or histamine antagonistic, properties. However, the toxicity of these first compounds led other investigators to search for drugs less toxic, and several compounds were evolved in France and later in this country. The antihistamine and anti-anaphylactic properties of each of the compounds were studied experimentally in animals. They were shown to prevent histamine-induced contractions of isolated tissue strips and were highly effective in blocking histamine-induced shock and in preventing fatal anaphylactic shock in hypersensitive animals. The degree of activity and the amount of each compound necessary to produce these effects in animals differs sometimes very widely. The activity in animals does not entirely parallel that in human beings.

Gilman,[2] writing on the pharmacology of drugs in allergic conditions, expresses the opinion that the term "antihistaminic" is a poor one to apply to these drugs, as epinephrine is the true physiologic histamine antagonist. He contends that since the "antihistaminic" compounds do not by themselves cause a prominent degree of muscular relaxation or have any effect on peripheral vasculature, we are dealing not with a physiologic histamine antagonist but with a type of blocking agent. The mechanism of action of this blocking agent is similar to that by which atropine can block the effects of acetylcholine or of cholinergic nerve impulses. Gilman proposes the term "histaminolytic" as more appropriate for these compounds.

The histaminolytics have now been used in a great many cases of various allergic diseases, and their therapeutic usefulness as adjuvants is established. Their paradoxical action, however, still needs to be explained. They will relieve only some allergic symptoms and not others, and in some cases, the percentage of relief obtained is small or absent. Gilman explains this by advancing the hypothesis that when histamine is released as a result of the reaction between antigen and antibody, the site of the release is probably directly within the effector cell, and therefore cannot be effectively

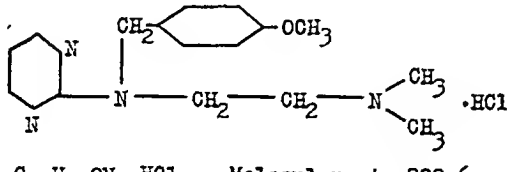
From the Division of Allergy, Department of Medicine, Long Island College Hospital.
Neohetramine was furnished through the courtesy of Nepera Chemical Co., Inc., and is now distributed by Wyeth, Inc.

blocked. The blocking action of a drug can only be effective when histamine comes to the cell by way of the circulation.

The basis of this hypothesis is that histamine is the sole chemical mediator in the antigen-antibody reaction. If the release of histamine is within the effector cell and the histaminolytic cannot block it, how then does effective blocking take place in some instances, and how are some symptoms in an allergic condition ameliorated while others are left untouched? The hypothesis is thus not entirely adequate, and further explanation of the action of the histaminolytics is needed. It was expected that the antihistaminics, by their blocking action of histamine, would serve as a further proof of this theory.

It seems, however, that histamine is not the sole mediator in the reaction, and several investigators have already advanced the possibility of more than one chemical substance being involved. Warren and Dixon,[4] in their antigen tracer studies, proved that the cause of death in guinea pigs from intravenous injection of histamine differs from the cause of death following anaphylactic shock as a result of antigen-antibody reaction. Death from histamine injected intravenously is caused solely by a marked contraction and thickening of the bronchial smooth muscle coat, while the bronchial obstruction in anaphylactic shock, resulting from antigen-antibody reaction, is due to massive edema of the loose bronchial collagenous connective tissue. In view of the above, the original conception of the mechanism in allergy seems to be controversial.

This report is on the clinical evaluation of Neohetramine, one of the histaminolytic drugs developed in this country. Neohetramine is 2-(N-dimethylaminoethyl-N-p methoxybenzyl)-aminopyrimidine monohydrochloride. It is a stable, crystalline, white compound which melts at 173° C., dec., and has the following chemical structure:



$C_{16}H_{22}ON_4 \cdot HCl$ Molecular wt. 322.6

It is highly soluble and relatively stable in aqueous solution. Concentrated solutions are slightly acidic; for example, 1 and 20 per cent solutions exhibit pH values of 5.7 and 4.5, respectively. These solutions may be adjusted to pH 7.0 without precipitation. A 0.2 molal solution of Neohetramine (6.35 per cent at 27° C.) is approximately 45 per cent dissociated and is isotonic with mammalian serum.

Scudi, Reinhald and Dreyer[3] have studied the pharmacologic characteristics of Neohetramine experimentally in animals. In their study of acute toxicity, they found that in mice the oral LD_{50} of Neohetramine is

approximately twice as high as the intraperitoneal LD_{50}, and in guinea pigs, five times as high. In a chronic toxicity study, Neohetramine was administered to 105 weanling rats, either by way of diet, 50 to 200 mg./kg. or subcutaneously, 10 to 20 mg./kg. twice a day for a period of ninety-one days. The animals exhibited normal growth and a complete absence of morphological blood changes or organ pathology.

Neohetramine showed marked activity against the capillary, bronchiolar, local vasodilator and smooth muscle and vasodepression actions of histamine. In actively sensitized guinea pigs, protection was afforded with as little as 1 mg./kg., but larger doses gave no significantly greater protection. In guinea pigs passively sensitized by intraperitoneal injection of 0.5 c.c. of antihorse rabbit serum, good protection was obtained in pre-animals with a dose of 5 mg./kg. No protection against local anaphylaxis (Arthus phenomenon) and anaphylaxis in isolated tissue was noted. Five to ten times as much drug was required to protect guinea pigs against anaphylactic as against histamine shock.

In addition to its histamine antagonistic action, Neohetramine exhibits also several other pharmacologic properties. In low concentrations it exerts a mild or no depressant action on smooth muscle, but in high concentration, it induces contractions. It does not potentiate the action of epinephrine and does not alter sympathetic responses. In the eye it produces a transient congestion, accompanied by local anesthesia comparable to procaine. It has slight atropine-like properties, shown by its ability to depress salivary secretion, and it produces some ventricular depression, bradycardia and transient lowering of blood pressure.

CLINICAL STUDY

The present study deals with the use of Neohetramine in 111 cases. This group comprised the following: hay fever, fifty-three cases; vasomotor rhinitis, twenty-two cases; bronchial asthma, twenty-four cases; chronic urticaria, five cases; allergic eczema, six cases; and pruritus, one case. The dose generally used was 50 mg. one to four times a day; though in many cases, 100 mg. three to four times a day was necessary to relieve the symptoms. The amount of the drug given, and the number of doses, had to be adjusted in many individuals according to their individual requirements. In patients benefited by Neohetramine, relief of symptoms or improvement occurred in fifteen minutes to one hour. Several of the patients in this series have taken from 300 to 400 mg. daily for three to four months without any abnormal changes in the blood count, blood chemistry or urine.

Hay Fever.—All hay-fever patients received pre-seasonal hyposensitization, and only those who had not received complete relief of symptoms were given Neohetramine. The response to Neohetramine could be readily evaluated. If relief occurred, it was usually definite within fifteen to thirty

TABLE I. RESULTS OF TREATMENT OF PATIENTS WITH NEOHETRAMINE

Allergic Condition	Number of Cases	Relief	No Relief	Percentage Relieved
Hay fever (ragweed)	41	29	12	70.7
Hay fever (timothy)	7	5	2	71.4
Hay fever (trees)	5	4	1	80.0
Vasomotor rhinitis	22	14	8	63.5
Bronchial asthma	24	10	14	41.7
Allergic Eczema	6	1	5	16.7
Chronic Urticaria	5	3	2	60.0
Pruritus	1	1	0	100.0
Totals	111	67	44	60.4

TABLE II. NEOHETRAMINE (111 CASES)—SIDE REACTIONS (8 CASES—7.2 PER CENT)

Side Reaction	Number of Cases
Drowsiness	2
Dryness of mouth	1
Nausea	1
Bitter taste	1
Tiredness	1
Headache	1
Restlessness	1
Marked nervousness	1
Aggravation of Asthmatic attack	1

minutes and was lasting, making the patient comfortable from several hours to the entire day, frequently on only one or two tablets a day. Symptomatic relief occurred in thirty-eight of fifty-three cases (71.7 per cent).

Vasomotor Rhinitis.—Twenty-two patients with vasomotor rhinitis were treated with Neohetramine. Various forms of therapy, such as elimination of foods and avoidance of inhalants that gave positive skin reactions, vaccine and dust injections, specific hyposensitization and local therapy, were previously given to these patients without relief. When Neohetramine was given in addition, fourteen (63.5 per cent) obtained relief and eight (36.5 per cent) obtained no relief.

Bronchial Asthma.—Of twenty-four patients with bronchial asthma, ten (41.7 per cent) were relieved and fourteen (58.3 per cent) obtained no relief. In some cases the relief obtained was better than with several other antihistaminics, including Benadryl and Pyribenzamine.

Allergic Eczema.—Neohetramine was given to six patients with allergic eczema. One was relieved and five were not. The one who obtained relief was a chronic case in which all forms of local applications, and later Benadryl, gave no relief. Both the itching and the rash completely disappeared after one week's time on 50 mg. of Neohetramine four times a day.

Chronic Urticaria.—In five cases of chronic urticaria three (60 per cent) were relieved and two (40 per cent) were not. One of the patients not relieved by Neohetramine was not relieved by any of the antihistaminics in use now.

Pruritus.—Neohetramine was administered in one case of generalized pruritus and gave complete relief.

SIDE REACTIONS

Of the 111 patients treated with Neohetramine, eight (7.2 per cent) complained of side reactions. Two discontinued the use of the drug—one on account of severe nausea, and the other because of the increase of the asthmatic symptoms one-half hour after the taking of 50 mg. of Neohetramine. Six patients had transitory symptoms: dryness of the mouth; drowsiness at first, which disappeared on further use of the drug; nausea and bitter taste in the mouth; nervousness, headache and restlessness.

SUMMARY

A group of 111 patients with various forms of allergy were treated with Neohetramine. In this group symptomatic relief occurred in sixty-seven patients (60.4 per cent), while forty-four patients (39.6 per cent) obtained either slight or no relief. Side reactions occurred in eight cases (7.2 per cent) of the group of 111 patients.

CONCLUSIONS

Considering the favorable results in 60.4 per cent of the 111 cases, and the very low and mild toxicity, Neohetramine appears to be a valuable drug for use in the symptomatic relief of a variety of allergic diseases.

REFERENCES

1. Fourneau, E., and Bovet, D.: Arch. internat. de pharmacodyn. et de therap., 46:178, (Oct.) 1933.
2. Gilman, A., Ph.D.: The pharmacology of drugs used in allergic conditions. J. Allergy, 19:281, (Sept.) 1948.
3. Scudi, J. V.; Reinhard, J. F., and Dreyer, N. B.: Pharmacologic characteristics of Neohetramine, a new antihistaminic drug. III. J. Allergy, 19:184, 1948.
4. Warren, S., and Dixon, F. J.: Antigen tracer studies and histologic observations in anaphylactic shock in the guinea pig. Am. J. M. Sc., 216:136-145, (Aug.) 1948.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

A joint meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy and the Hansel Foundation was held at the Hotel Sheraton, St. Louis, Missouri, May 30-June 4. On the first day there were guest speakers, a luncheon and round table discussion, and a banquet in the evening. The remaining four days were devoted to intensive, practical instruction in allergy as related to otolaryngology. The course was well attended. An interesting feature was the participation of the registrants in all practical demonstrations, including the various methods of skin testing, cytologic studies, pollen counting and methods of pollen survey. More of this type of instruction in allergy is needed.

SKIN REACTIONS

XVI. Comparison of Antihistaminic Action of Pyribenzamine and Epinephrine Introduced into Human Skin by Electrophoresis

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RECENT emphasis on the use of drugs of the Pyribenzamine type for the inhibition of the whealing and flare reactions in the human skin, has, to a certain extent, led to the neglect of the fact that epinephrine is, if not the most, one of the most powerful antihistaminic drugs, as measured by effect rather than by pharmacodynamic *theory*. In order to aid in the evaluation of the therapeutic possibilities of drugs similar to Pyribenzamine, and of the sympathomimetic amines like epinephrine, it was decided to compare the effect of skin depots of Pyribenzamine hydrochloride and of epinephrine phosphate, administered by electrophoresis, on the production of wheals by histamine superimposed on areas previously treated by Pyribenzamine and by epinephrine.

METHOD

The methods previously developed were utilized.[2,3,5,6] The current density at the positive pole varied between 0.3 and 0.5 milliampere per square centimeter. Canton flannel was saturated with the solutions tested and applied with gentle pressure. As previously described, the electrodes touching the skin were always in contact with aluminum foil. In general, the electrodes were applied to the skin from three to five minutes. The technique developed to study the effect of depots of atropine on the vasodilatation of the skin by mecholyl, was applied with this exception: When epinephrine is introduced into the skin by electrophoresis, in a few minutes the initial irritation due to the introduction of this drug disappears and a clearly blanched area is observed. The type of blanching is illustrated in Figure 1. The blanched area is surrounded by a flare. It is of some interest that this flare resembles the flare produced by histamine itself. As previously observed, with higher concentrations of epinephrine, white psuedopods are observed which are due to the lymphatic escape of the epinephrine into the dermis.[4]

EXPERIMENTS

A typical experiment is illustrated in Figures 1, 2 and 3. Figure 1 represents the effect of 1:10,000 solution of epinephrine phosphate introduced into the forearm electrophoretically with a current density of approximately 0.3 milliampere for 5 minutes. Figure 2 is a photograph of the result of superimposing on, and at right angles to, the area treated

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This research has been aided in part by a grant from the Josiah Macy, Jr., Foundation, New York City, and by the Foundation for Research in Pulmonary Disease, New York, N. Y.

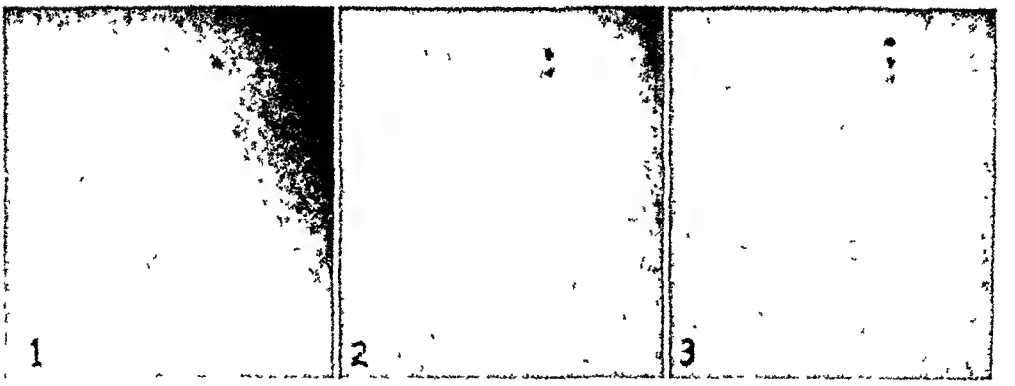

Fig. 1. 1:10,000 epinephrine was introduced into the forearm electrophoretically with a current density of approximately 0.3 ma. for five minutes. Started at 11:00 a.m. There is a flare about the blanched area. Photograph was made at 11:15.

Fig. 2. 1:50,000 histamine introduced with a rectangular electrode, half of which was placed over the site where the epinephrine was introduced. The histamine was electrophoretically introduced at a current density of about 0.3 ma. for two minutes. Area over epinephrine shows slight reddening and slight wheaing after five minutes. Entire area is surrounded by flare. Experiment was started at 11:21 and picture was taken at 11:30.

Fig. 3. Photograph taken at 11:45 shows disappearance of histamine reaction and reappearance of blanched area surrounded by flare. This is the "restoration" effect of epinephrine.

with epinephrine, an electrode delivering a 1:50,000 solution of histamine phosphate. This photograph was taken thirty minutes after the epinephrine had been introduced. It illustrates the flare, both around the blanched areas and around those treated only with histamine. In this experiment a fairly distinct elevated wheal was formed over the blanched area. If a stronger solution of epinephrine is used (say, 1:1,000), the whealing is not so marked. However, this histamine reaction is transient. The phenomenon that took place thirty minutes after the introduction of the histamine is illustrated in Figure 3. Although the wheal outside the blanched area persisted, the epinephrine blanching reaction reappeared at the histamine site, with the blanched area almost complete at the original site. This reappearance of the blanching, forty-five minutes after the introduction of histamine, is spectacular. It indicates that even though the blood vessels responded by dilatation and changed permeability to histamine, sufficient epinephrine remained at the site to reassert itself pharmacologically and to restore pharmacologically the antihistamine status of the area treated with epinephrine. It has been shown that histamine *increases* absorption and this phenomenon is unexpected. This "restoration" effect, in all likelihood, is more characteristic of certain of the sympathomimetic amines. Whether it will occur in areas treated with Pyribenzamine is not known.

A striking example of this "restoration effect" was observed when 1:1,000 epinephrine phosphate was observed for three minutes (current density 0.3 milliampere) with 1:1,000 histamine superimposed similarly to the technique depicted in Figure 2. Vasodilatation in the epinephrine-blanched area treated with histamine persisted more than four hours. But as the reddened area disappeared, *the blanching due to the epinephrine*

was restored at the site five hours later.* It is of particular interest that the control part of the histamine wheal often apparently disappeared before that part in the blanched areas when weaker epinephrine solutions were introduced. It is conceivable that under certain circumstances the epinephrine may retard absorption of histamine.

Solutions of 10 per cent and 5 per cent Pyribenzamine hydrochloride produce similar inhibition reactions.[1] Initially, after the introduction of Pyribenzamine hydrochloride by electrophoresis, there is an erythema at the site and small papules form about the pores of the skin. It takes some time for this reaction to disappear, usually about one and one-half hours. As previously shown for atropine and histamine, depots of the drug are formed in the skin. The whealing response to 1:50,000 histamine is essentially inhibited by a depot of 10 per cent Pyribenzamine. In addition, the Pyribenzamine site apparently inhibits the flare. This is not true of epinephrine because the epinephrine itself sets up the flare. It is of interest to compare the epinephrine effect with the Pyribenzamine effect.

A semi-quantitative comparison of the two effects leads to the conclusion that a solution of 1:10,000 epinephrine phosphate is essentially as effective as 1:10 Pyribenzamine hydrochloride with our technique. In addition, there is the "restoration effect" of the epinephrine which occurs after the histamine wheal has disappeared. The epinephrine is about 1,000 times as effective an antihistaminic drug as Pyribenzamine when used electrophoretically. The practical significance of this wide difference will be taken up in the discussion.

DISCUSSION

These experiments were undertaken in an attempt to evaluate the possible advantages to be gained by using Pyribenzamine by electrophoresis or Pyribenzamine in an ointment form in the dermatoses instead of epinephrine. According to these observations, Pyribenzamine has no particular advantage over epinephrine in the dermatoses as far as topical therapy is concerned. It is ordinarily assumed that a histamine-like substance is responsible for many of the lesions and of the symptoms. It appears much more logical to use epinephrine by electrophoresis in suitable concentrations or an epinephrine ointment. Epinephrine ointments at one time found a sphere of usefulness in the dermatoses. However, the emphasis given to the drugs of the Pyribenzamine type has caused the usefulness of epinephrine ointment to be neglected. One of us (H.A.A.), has been studying epinephrine ointments of different concentrations with different vehicles. In view of the systemic effects of epinephrine, it would not be desirable to use high concentrations over extensive areas where there has been a good deal of scratching because

*It seems possible that the histamine action was prolonged over the blanched area due to the vasoconstriction of the epinephrine.

of rapid absorption. However, cautious employment of high concentrations over small areas is feasible. Well-demarcated areas of vasoconstriction are observed over freshly scratched areas. The blanching may persist for hours. The effect of 0.05 per cent epinephrine ointment after one hour is illustrated in Figure 4. These data will form the basis of a subsequent report.

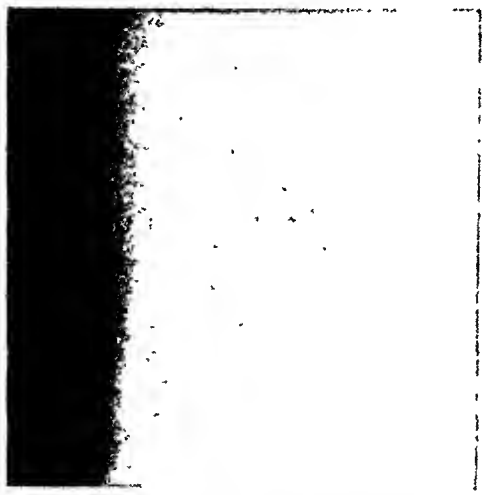

Fig. 4. Blanching produced by 0.05 per cent epinephrine ointment about scratch marks after one hour.

SUMMARY

Epinephrine is one of the most powerful antihistaminic drugs, as measured by effects rather than by the definition in pharmacodynamic theory. In order to evaluate the therapeutic possibilities of drugs similar to Pyribenzamine and of epinephrine in the skin, the effect of skin depots of Pyribenzamine hydrochloride and of epinephrine phosphate, administered by electrophoresis, on the production of wheals by histamine superimposed on areas previously treated by Pyribenzamine and epinephrine, was studied. It was found that, weight for weight, epinephrine was approximately 1,000 times as effective as Pyribenzamine under the conditions of experiment. In addition, a new effect, the "restoration" effect of epinephrine, is described. This restoration effect is the reappearance of epinephrine blanching as long as five hours after the histamine has been administered within the blanched area. It is pointed out that the strong antihistaminic action of epinephrine makes clinical trial of epinephrine ointments in the allergic dermatoses a possibility which should be investigated in detail. The "restoration" effect accounts for the prolonged and effective action of topical therapy with epinephrine, as in aerosol therapy of the lungs.

(Continued on Page 358)

ALLERGY AND THE TONSIL PROBLEM IN CHILDREN

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IT is important that the pediatrician, the allergist and all other medical men who treat children should review the tonsil and adenoid problem in its relation to allergic disease. The tonsils and adenoids in children receive more attention from the medical profession than any other organ. This study is primarily concerned with those patients who had their tonsils and adenoids removed without relief of the original symptoms for which the operation was performed. Re-examination revealed that the tonsils or adenoids "grew back." These children suffered from symptoms indicating irritation or obstruction in the upper or lower respiratory system, usually of a chronic, periodic nature. This investigation was initiated twenty years ago at the Children's Clinic to discover whether tonsils and adenoids "grew back" due to faulty surgical technique or to some other unknown cause. The answer to the problem was very different from that which had been anticipated. This resulted in a reversal of our plan of treatment. The allergic problem was recognized and treated first; then an operation was performed, if still necessary.

The plan was to record the details of the operation, label and preserve all the tonsil specimens removed at operation. When a patient returned complaining of the same symptoms for which he had previously been operated upon, or if, on examination, pieces of lymphoid-tissue were found in the tonsil fossae or postnasal space, the patient's previously removed and preserved tonsils were re-examined. Careful search was made to see if any of the capsule or tonsil was missing that might have served as a focus for a regrowth of tissue. The tonsils were always complete. After a thorough review of these cases, one salient conclusion was definite—*most of these patients had an allergic basis for their symptoms which had not been recognized prior to operation.* The operation had failed because the tonsils had been removed to correct allergic symptoms.

Patients in this series who returned for further treatment usually had the same complaints which had been the indications for the previous operation.

The cardinal symptoms were of two types: (1) The mother stated that the child still had "one cold after another,"[3] usually without fever; that his nose was always "stopped up" and breathing was difficult because he was a mouth breather; that a watery discharge was often present, and that he sniffled and blew his nose frequently, more so early in the morning. (2) Many of these colds were associated with a hacking or clearing of the throat. They often terminated in a deep, hard, dry cough which was more fre-

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quent during the night. Recurrent attacks of croup with or without a respiratory infection were common complaints.

A persistent hacking, tiring cough, often with wheezing, and difficult breathing may accompany the above symptoms. A low-grade fever sometimes persisted for months and had to be differentiated from chronic infections such as tuberculosis, sinusitis and rheumatic fever! A few patients had been told by other physicians that the tonsils and adenoids had "grown back" and should be removed again.

The patients whose tonsils "grew back" revealed that breathing (through the nose) was difficult except when the mouth was open. This was the most common postoperative complaint. The parents frequently asked if the adenoids had been removed! Physical examination of such patients may be normal to inspection. Having the patient blow each side of the nose alternately will often reveal some stuffiness in one or the other nostril due to postnasal edema which cannot be seen by ordinary examination. Acute edema of the anterior turbinates may or may not be present. The fact that the congested nasal passages clear up at times, and the patient breathes normally, then becomes stuffy at night, indicates that there is no definite constant obstruction, such as would be caused by a large mass of adenoid tissue. The type of stenosis due to large adenoids is usually of the same degree day or night and from day to day, in contrast to the intermittent congestion of the allergic child.

This study is composed of two groups of patients: the author's patients who were known allergic children and who had their tonsils and adenoids removed at the Children's Clinic, and those patients in whom the operation was performed by other physicians elsewhere. The diagnosis of allergy in this latter group was usually made postoperatively. Some observations relating to the children in this series will be presented (Table I). One hundred and thirty-six allergic children had their tonsils and adenoids removed. These children had careful pediatric treatment from birth and were known to be allergic.[2] They also had definite indications for removal of their tonsils and adenoids, which were the same as for nonallergic children. Only four children in this group (3 per cent) had recurrent growth of lymphoid tissue in the tonsil fossae or adenoid area. None of these four children had any previous specific allergic treatment and all were under the age of three years. Both factors may predispose to regrowth of lymphoid tissue.

The tonsillar fossae are not involved in the above syndrome nearly as often as the postnasal spaces. Due to the rather large postnasal adenoid spaces, small amounts of regrowths of lymphoid tissue in this area do not cause noticeable symptoms. If this lymphoid hypertrophy occurs in front of the eustachean tubes, partial deafness may occur. This will improve as the patient's allergic symptoms retrogress. Only a small percentage, as mentioned previously, will have tissue regrowths in the tonsil

TABLE I. TONSILLECTOMY AND ADENOIDECTOMY IN ALLERGIC CHILDREN

Diagnosis Made (Allergy)	No. of Allergic Cases	Diagnosis Known before T.&A.	No. of Cases "Tonsils Grew Back"	Per Cent	No. of Cases Operated upon Twice
Before T.&A.	136	136	4	3	0
After T.&A.	60	10	14	23	6

fossae. It is possible and probable that in some cases incomplete operation may have been the cause, but due to the high degree of training and skill of present-day surgeons this has been a rare occurrence in our observation. The fossae, if seen during an acute infection, may reveal rather prominent reddish swollen lymphoid tissue, often appearing similar to granulation tissue. This is usually located in the lingual area, under the anterior pillar or in the middle of the fossa. These pieces of tissue, when quiescent, will shrink considerably, often resembling scar tissue. They may become infected, the same as any other portion of the throat. A granular or nodular pharynx is often present, with various sized pinhead to pea-sized, roundish, raised areas scattered in the pharynx. The lateral walls are frequently studded with new growths of lymphoid tissue. These findings should always suggest an allergic background. Allergic disease predisposes to hyperplasia of lymphoid tissue especially in the nasopharynx.

Regrowth of tissue in the fossae was noted as early as five months after operation. The operation did not relieve or cure the patient of the symptoms from which he suffered. Surgery of the tonsils and adenoids when performed for the relief of allergic conditions, particularly the various manifestations of hay fever or asthma, usually results in failure. Piness,[10] in 1925, voiced this warning in an article entitled, "Allergy, A Non-Surgical Disease of the Nose and Throat." It is true that there may be a temporary improvement in the asthmatic state. This is possibly due to a shock-like effect of necrotic tissue in the throat or of the anesthetic (Feinberg).[6] Hansel[7] has stated that many allergic patients are considered as having infection, because of the absence of hay fever or asthma at the time of examination or operation. The indications for tonsil and adenoid surgery in the allergic child are the same as those in children without nasal allergy. If the family is frankly told that the operation may improve the child's general health but will not materially influence the allergic symptoms, better future relations will exist between the family and the physician.[5] Evatt has stated that since there are approximately eighty-five deaths a year from tonsillectomy in children under fifteen years, and since this type of surgery is not without danger, it should be regarded as a major operation. In allergic children, with pathologic tonsils, in approximately 50 per cent of these candidates for tonsillectomy, an operation will not be necessary once the allergic symptoms are successfully treated. The tonsil and adenoid tissues will shrink or atrophy. This is a common observation among allergists and pediatricians.

In the second group of sixty children, only ten were suspected of having hay fever or asthma. In this undiagnosed and untreated (for allergy)

group there were fourteen patients (23 per cent) whose "tonsils grew back." Six children (10 per cent) also had their tonsils and/or adenoids operated upon twice, and one child had three operations. All retained their original symptoms. Of the ten children in whom the diagnosis of allergy was suspected prior to operation, only one was improved. None of this group had been treated previously for allergy. In the entire group of 196 cases, forty-three children had been operated upon between the ages of two and three years, and 113 before five years of age. The remaining forty were from five to twelve years of age. The indications for operation were the same for the known allergic group as for any nonallergic child.

COMMENT

The results of this study have indicated that when tonsils and adenoids "grow back," it usually occurs in allergic individuals in whom the diagnosis was not known prior to the operation.

The differential diagnosis between the infectious and allergic cold is important. Cohen and Rudolph[1] in 1931 very ably called attention to this problem. The author[3] had previously commented on the fact that allergy as the cause of frequent colds and chronic coughs in children is overlooked more than any other common disease. Hansel[8] has contributed a simple but very excellent test for diagnosing the allergic cold. Nasal smears will frequently show an excess of eosinophiles, which is pathognomonic of allergic disease. No nasal case should be dismissed as nonallergic until repeated smears have shown very few eosinophiles.

Many observers have noted the relationship between tonsil and adenoid removal and allergy. Peshkin[9] investigated 100 asthmatic children. Seventy-two had had tonsil and adenoid operations; in twenty the tonsils had been removed previously to the onset of the asthma, and in fifty-two they had been removed after the onset of the asthma. In a large percentage of these cases, the operation had been performed for the relief of frequent colds without satisfactory results. Temporary relief of asthma was noted in only one case. Bullen[1] studied 1,000 children who had tonsillectomies and 1,000 controls. He concluded that tonsillectomy does not aid in improving the effects of treatment of respiratory allergy. Hansel sums up this problem by stating that the clinical course of the allergy is much the same whether the tonsils are or are not removed. The Johns Hopkins group[11] studied thirty-four asthmatic children; many with partial deafness. Sixteen (47 per cent) had previous tonsil and adenoid operations, eighteen (53 per cent) did not have operations. All had asthma and lymphoid hyperplasia in the postnasal spaces. All of these patients were allergic children. They were relieved by treatment with a nasopharyngeal radium applicator. In some children who are allergic, a tonsillectomy and adenoidectomy are definitely indicated for other reasons. With careful control of the allergy, the occurrence of complications could be avoided with rea-

sonable safety. It is a common observation that this operation when performed during the pollen season will often aggravate pre-existing pollenosis and may precipitate asthma.

Some contraindications for tonsil and adenoid surgery are suggested: (1) If the patient has a chronic "running nose," seasonal or perennial, which is more or less persistent. This may be present in a child who snores, keeps his mouth open most of the time, especially at night. The history often emphasizes a "stuffy nose" usually worse during the night and upon arising, which clears up during the morning. (2) A history of frequent colds, "one after the other," especially in the winter, and a chronic cough, often worse at night. The cough is often aggravated by fatigue or exercise. The symptoms did not respond to any previous treatment. (3) So-called "chronic sinus infections" with or without migraine type headaches. (4) In children whose tonsils and adenoids "grew back" and who still retain their original symptoms.

SUMMARY AND CONCLUSION

Children whose tonsils and adenoids "grew back" following tonsillectomy and adenoidectomy were found to be those who had undiagnosed and untreated allergic disease. When the allergic symptoms are properly treated in children who require tonsil and adenoid removal, the incidence of regrowth of lymphoid tissue in the tonsil fossae is negligible—3 per cent compared to 27 per cent in undiagnosed, untreated, allergic children. All children in this category should have the benefit of a thorough allergic study. Symptoms of allergic disease are usually not relieved by tonsil and adenoid removal. Early diagnosis and specific thorough treatment is the most effective therapy for symptoms due to allergic disease.

REFERENCES

1. Bullen, S.: The effect of tonsillectomy in allergic conditions. J. Allergy, 2:310, 1931.
2. Clein, N. W.: The growth and development of allergy, a ten-year study of 100 children from birth to adolescence. Ann. Allergy, 3:1-11, (Jan.) 1943.
3. Clein, N. W.: Allergy as the cause of frequent colds and chronic coughs in children. Northwest Med., 35:347, (Sept.) 1936.
4. Cohen, M. B., and Rudolph, J. A.: Allergic and infectious conditions of the upper respiratory tract in children; differential diagnosis. J.A.M.A., 97:980, (Oct.) 1931.
5. Evatt, C. W.: What removal of tonsils will and will not do. South. M. & Surg., 104:249, (May) 1942.
6. Feinberg, Samuel: Allergy in Practice. Pp. 539-583. Chicago: Year Book Publishers, 1944.
7. Hansel, F. K.: Allergy of the nose and paranasal sinuses. Pp. 538, 544, 545. St. Louis: C. V. Mosby, 1936.
8. Hansel, F. K.: Observation on the cytology of the secretions in allergy of the nose and paranasal sinuses. J. Allergy, 5:357, 1934.
9. Peshkin, M. M.: Asthma in children. III. The incidence and significance of various diseases and infections, and of tonsillectomy and adenoidectomy. Am. J. Dis. Child, 33:880, 1927.
10. Piness and Miller: Allergy—a non-surgical disease of the nose and throat. J.A.M.A., 85:339, 1925.
11. Ward, A. T., Jr., et al.: Asthma in children—treatment with radium nasopharyngeal applicator. J.A.M.A., 133: 1060, (Apr.) 1945.

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A STUDY OF THE INCIDENCE OF AIR-BORNE FUNGI IN THE CITY OF RIO DE JANEIRO

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A STUDY of the air-borne molds was made to elucidate local problems concerning allergy.

The complete investigation of the allergy caused by inhalation of fungus spores consists of: (1) qualitative and quantitative identification of the Eumycetes of the surroundings, and the correlation of meteorological and seasonal fluctuations; (2) preparation of respective allergens with the verification of the allergic patients' sensitivity to them. In this paper we shall deal only with the qualitative and quantitative identification stated in item (1).

After reporting the results of two months of air observations in a previous publication,[5] we continued these studies over a period of two years, from September, 1943, to August, 1945.

METHOD

The Petri plate method is preferable to the slide method. Petri plates, 10 cm. in diameter and 2 cm. high, containing Sabouraud's conservation medium,* were exposed horizontally outside a window for a period of fifteen minutes (from 11:45 a.m. to 12:00 noon) at the Hospital São Francisco de Assis, Rio de Janeiro, Brazil.

During the first year (September, 1943, to August, 1944) the plates were exposed once a week, and during the second year (September, 1944, to August, 1945) once every two weeks, following the procedure of Morrow, Prince and Lowe[4].

The plates were left at room temperature for three or more days until the colonies were sufficiently developed for their identification. Those which were not easily identified were transferred to tube slants of the same medium in order to observe and study further. New transfers were sometimes made using different media, and frequently slide cultures were employed. The same numbers were used for the tube cultures as were used for the original colonies on the Petri plates. By marking the reverse of the plate or by making a diagram (processo de decalque), numbers were matched, and colonies could be observed and studied in the tube and plate cultures simultaneously.

In this work we were concerned only with classification to the genus, which is considered of primary importance by Bernstein and Feinberg,[1] that determination of species has less importance in mold allergy. They

Read at the first annual meeting of the Sociedade Brasileira de Alergia, December, 1947.

*Glucose	40.0	Agar	30.0
Peptone	10.0	Water	1000.0

TABLE I

Molds	Number of Colonies	Per Cent
Yeasts	476	30.2%
Hormodendrum	261	16.5%
Rhodotorula	259	16.4%
Penicillium	226	14.3%
Aspergillus	127	8.0%
Fusarium	52	3.5%
Miscellaneous:		
Phoma	33	
Trichoderma	21	
Mucor	18	
Stemphylium	13	
Alternaria	10	
Monilia sitophila	9	
Helminthoporium	9	
Rhizopus	8	
Pestalozzia	8	
Acrothecium	8	
Scopulariopsis	6	
Nigrospora	5	
Gloesporium	5	
Chaetomium	3	11.1%
Oospora	2	
Robillardia	2	
Epicoccum	2	
Criptomela	2	
Cephalosporium	2	
Botrytis	1	
Nodulisporium	1	
Fusidium	1	
Periconia	1	
Coniosporium	1	
Septoria	1	
Trachysphaeria	1	
Acrostalagmus	1	
Acrostalagmus	1	

point out that in some instances cross neutralization has occurred even between different genera.

For the classification of fungi we followed Clements and Shear,[2] Olimpio da Fonseca Filho,[3] and Verlande D. Silveira.[6]

RESULTS

A total of 1,852 fungus colonies was found, of which 1,575 were classified, the remaining 277 lacking reproductive structures or other identifying characters.

The six most frequently found were: (1) yeast (Saccharomyces type), (2) Hormodendrum, (3) Rhodotorula, (4) Penicillium, (5) Aspergillus, and (6) Fusarium. Phoma, Trichoderma, Mucor, Stemphylium, Alternaria, Monilia sitophila, Helminthosporium, Rhizopus and others were also found.

Of the total 1,575 colonies, 30.2 per cent were yeasts, 16.5 per cent Hormodendrum, 16.4 per cent Rhodotorula, 14.3 per cent Penicillium, 8.0 per cent Aspergillus and 3.5 per cent Fusarium, the remaining 11.1 per cent including 27 different genera (Table I).

DISCUSSION OF FREQUENT MOLDS

Yeasts.—Whereas yeasts were encountered in large numbers, and represented a variety of forms, seasonal aspects were not apparent, except in the case of the Rhodotorulae.

Rhodotorula.—The Rhodotorulae, which represent 16.4 per cent of the total fungi, were found to have no well-defined seasonal variation, although this genus predominated during the months from May to October (Fig. 1).

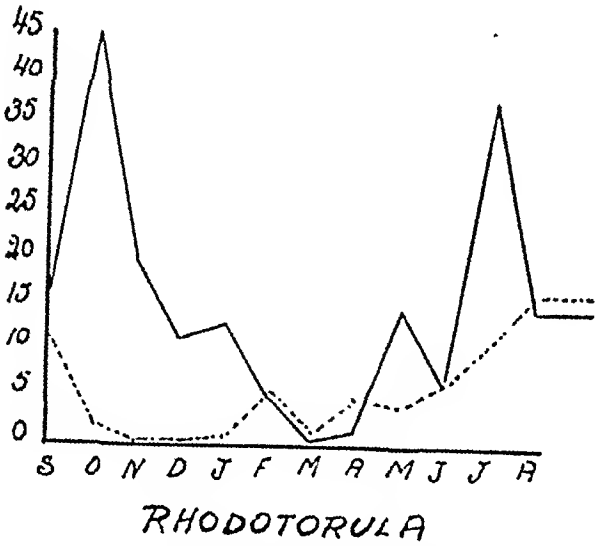

Fig. 1. Solid line represents 1943-1944; dotted line, 1944-1945.

Of the total found during each period during 1943-1944 and 1944-1945, percentages of 70.4 and 78.8, respectively, were identified from May to October. The months of highest incidence were July and October in the 1943-1944 period and August in the 1944-1945 period.

Homodendrum.—This genus showed the clearest seasonal variation, predominating also from May to October, that is, during the end of autumn and winter and beginning of spring in South America (Fig. 2).

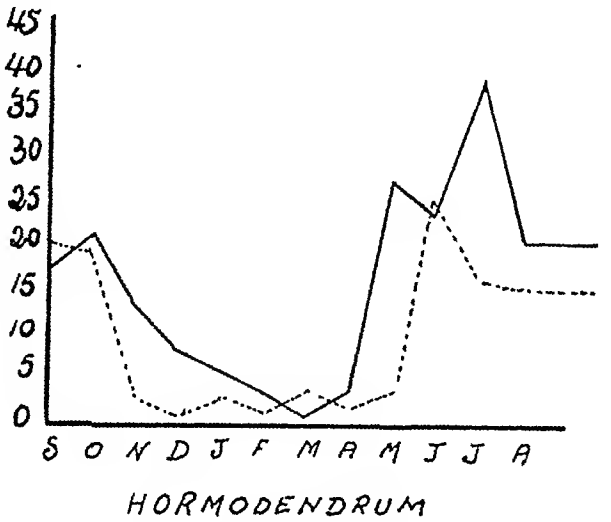

Fig. 2. Dotted line represents 1943-1944; solid line, 1944-1945.

Of the total of the two periods, 83.5 per cent were found during these months. The months of highest incidence were May in the 1943-1944 period and July in the 1944-1945 period. Hormodendrum represents

16.5 per cent of the total fungi and 28.8 per cent of the six more frequently found molds.

Penicillium.—This genus was found with almost the same frequency in all the months of the year, with the exception of December and January

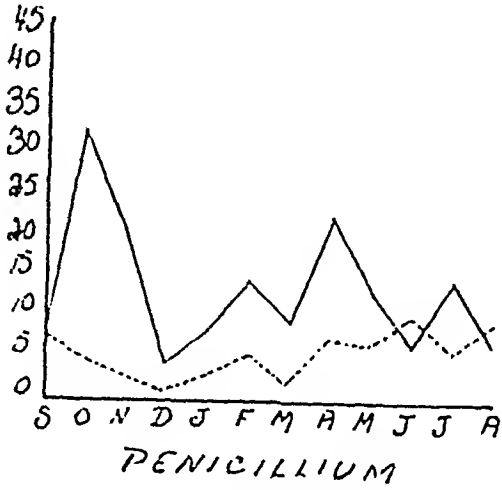

Fig. 3. Solid line represents 1943-1944; dotted line, 1944-1945.

when the number was quite reduced. That is, it had almost the same seasonal variation as Rhodotorula and Hormodendrum, but started earlier and finished later (Fig. 3). The months of highest frequency were October and April in the 1943-1944 period and November and July in the 1944-1945 period. The Penicillium represented 14.3 per cent of the total fungi found during the two periods.

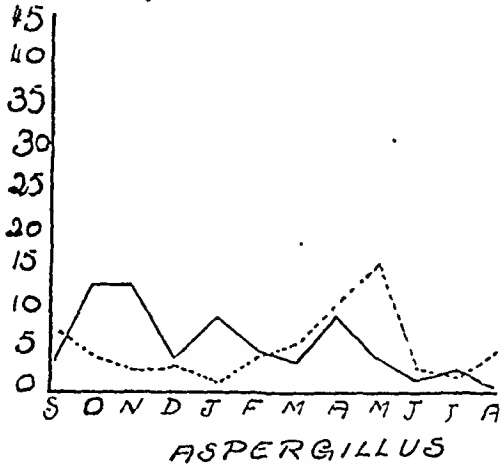

Fig. 4. Solid line represents 1943-1944; dotted line, 1944-1945.

Aspergillus.—There was a lack of seasonal correlation with this genus, since the distribution during the two years was quite uniform (Fig. 4). The lowest incidence was found during June and July in the two periods;

the highest during October and November in the 1943-1944 period and May in the 1944-1945 period. The Aspergilli represented 8.0 per cent of the total.

Fusarium.—Here, also, no seasonal influence was noticed. Fusarium represented 3.5 per cent of the total.

Miscellaneous.—The remaining fungi, which represent 27 different genera form 11.1 per cent of the total, i.e., Phoma, Trichoderma, Mucor, Stemphylium, Alternaria and others, and, although of only occasional occurrence, are noteworthy in that they show a qualitative picture. In regard to the undetermined molds, no seasonal variation was apparent.

The high monthly total counts of all fungi from June to October are a reflection of the corresponding high counts of Hormodendrum, and to a somewhat less degree, of Rhodotorula and Penicillium.

SUMMARY

From the study of the incidence of air-borne fungi in the city of Rio de Janeiro, Brazil, at the Hospital São Francisco de Assis, at first by weekly exposure of Petri plates during the 1943-1944 period and afterwards by semi-monthly exposure during the 1944-1945 period, we concluded that:

1. The most commonly found groups were Yeasts (Saccharomyces type), Hormodendrum, Rhodotorula, Penicillium, Aspergillus and Fusarium, making up 88.9 per cent of total fungi.

2. Seasonal incidence was noted particularly for Hormodendrum and also in the case of Rhodotorula and Penicillium.

3. Highest numbers and seasonal frequency coincide in the months from May to October, that is, from the end of autumn through winter to the beginning of spring in Rio de Janeiro, Brazil, South America.

4. This study is an attempt to aid the allergist of Rio de Janeiro and environs. Further studies of air-borne fungi should be made, and in more detail. These are in prospect. A study of the yeasts would be of interest.

REFERENCES

1. Bernstein, T. B., and Feinberg, S. M.: Air-borne fungus spores. Five years survey of daily mold spore content of Chicago air. J. Allergy, 13:233-241, (March) 1942.
2. Clements, F. E., and Shear, C. L.: The Genera of Fungi. New York: 1931.
3. Fonseca Filho, O.: Parasitologia Medica. Parasitos e doencas parasitarias do homem. Tomo I. Rio de Janeiro: Guanabara, 1943.
4. Morrow, M. B.; Lowe, E. P., and Prince, H. E.: Mold fungi in the etiology of respiratory allergic diseases: Survey of air-borne molds. J. Allergy, 13:215-226, (March) 1942.
5. Passarelli, N.; Miranda, M. P., and Castro, C.: Cogumelos do ar na cidade do Rio de Janeiro. Revi. med.-cir. do Brasil, 52:173-182, (Jan.) 1944.
6. Silveira, V. D.: Licoes de Micologia. Rio de Janiero: Editora Kosmos, 1946.

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SINUSITIS, ALLERGY, AND BACTERIAL VACCINE

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THE purpose of this paper is to report certain clinical phenomena and discuss some possible implications and explanations. During more than twenty years the writer has found that hundreds of consecutive unselected cases of both infective and allergic sinusitis have been relieved, benefited, made comfortable, or controlled by an adequate dosage of sensitized mixed vaccine, properly given,* plus some increase of drainage by shrinking drops, used posturally. Concurrently, dependent symptoms such as nasal congestion, postnasal drip, headache, otitis, tonsillitis, laryngitis, bronchitis, asthma, and some skin rashes have cleared up. Mastoiditis has not developed, and operations have not been necessary. In addition to these objective changes, and where they were not demonstrable, the vast majority of patients so treated reported a definite improvement in their symptoms, often after various surgical and medical treatments had given no such relief.

As the late Sir Almroth Wright[15] so clearly argued some ten years ago, the classical method of statistical experimentation is a principle of strictly limited application which cannot always be used for testing the value of therapeutic methods. Fidler makes much the same point in his book, *Whither Medicine, from Dogma to Science.* However, in this case, if one wishes to compare a group of treated cases with a group of untreated cases, he can contrast the condition of several scores or hundreds of people over a period of months and even of years, who have suffered from sinusitis, with a group of individuals whose signs and symptoms become alleviated during a short period of treatment. The fact that the two groups are composed of the same individuals makes the statistical experimentation more accurate, because it rules out a great variety of confusing issues.

The following five case reports have been chosen from hundreds, *as examples only.*

Case 1.—J. P., an eleven-year-old girl, was seen on October 24, 1946, complaining of aching in the frontal region for more than a month and of her eyes giving some discomfort. She had been seen by an eye, ear, nose and throat specialist who exonerated the eyes and sinuses. Sometimes she had a slight earache. Her breath was usually malodorous. Her throat looked irritated, with some mucous discharge. She was given nasal drops and a course of vaccine. On November 1 she was feeling better after two inoculations. She continued to improve steadily under treatment. Seven months after the first visit, her mother reported that she was still doing very well and that the neighbors had noticed that she looked to be in much better health. The bad odor was gone from her breath.

Case 2.—Miss G. E., aged thirty, was seen on April 9, 1946, having been referred by an eye, ear, nose and throat surgeon. She had had chronic nasal blocking and throat soreness as long as she could remember. It was usually worse in winter.

*The exact method of vaccine treatment used is described in detail at the end of this paper.

Another eye, ear, nose and throat specialist had wanted to do skin tests but she had no time. She had considerable pharyngeal dropping, especially in the morning, and frequent headaches. A few skin tests were done. House dust showed 1-plus. About 1/50 c.c. of ordinary cold vaccine produced a similar wheal to that caused by the house dust. She was started on nasal drops and a course of vaccine. Three days later she said she felt better and that her throat felt better. There was continued improvement. On April 25 her voice sounded clearer, and although her throat used to fill up and be uncomfortable, it no longer did. On May 10 she was feeling much better. On some days her head was very clear. On May 31 she felt that her sinuses were much better.

This patient had a slight recurrence the latter part of October and received another course of vaccine. Again she responded very quickly.

Case 3.—M. H., aged twenty-four, stated on August 8, 1942, that for over five years she had been troubled by blocking of the nose, pharyngeal dropping, headaches, tiredness, et cetera, and that she had begun to lose weight. A tonsillectomy five years earlier had given some temporary relief. She was started on a course of nasal drops and vaccine, and felt better five days later. She continued to improve. On September 12 she came in for the sixth dose of vaccine, feeling much better. Her nose was not so blocked and her head not so tight. On October 19 she reported that she still was very well and for all practical purposes seemed cured.

Case 4.—W. W. C., a fifty-year-old man, was seen on January 15, 1943. He had had nasal congestion for two years, following an episode of "flu." He was given nasal drops and only one inoculation of vaccine. He returned on June 17 to report that he had been much better for a month after the January treatment. He improved during June and July under a course of vaccine, until on July 15 he reported that he was having no further trouble with his sinuses.

Case 5.—H. B., a twenty-one-year-old man, seen on October 10, 1947, complained of having a head "cold" almost constantly since he had joined the Air Force in 1945. He had a headache, stuffed nose and pharyngeal dropping. When seen, he seemed to have an acute "cold." He was started on treatment with nasal drops and vaccine. Four days later he said that the headache was gone and his nose was not so "stuffy." On October 23 he felt much better. When he came for his sixth inoculation on November 7, he considered that he was so greatly improved he would not need to return unless the condition reoccurred.

It does not seem that any useful purpose will be served by describing more examples. Some patients developed reoccurrences or new infection. These usually responded more quickly than they had the first time. A few patients did not seem to retain their state of improved immunity (or hypo-sensitivity) for more than a few weeks. These patients were usually kept comfortable by an inoculation of the optimal dose once a month, until they gradually developed a more prolonged resistance.

Is it possible to suggest a theory to explain both infective and allergic sinusitis which is consistent with the phenomena described? The following comments seem reasonable to the writer as a working hypothesis.

Von Pirquet[11] proposed the term allergy, including bacteria among the many causes. Quoting various workers, he concluded, "Immunization and hypersensitivity therefore can be connected most intimately with one another.

"For this general concept of the *changed capacity to react, I suggest the term allergy.*"

Probably because research workers attempted to separate the sensitivity type of reaction from the immunity type of reaction *for purposes of study,* it became the vogue to forget and ignore Von Pirquet's observation, and to attempt both diagnosis and treatment of the body's reactions on the underlying assumption that this artificial separation also occurred in nature. However, more and more, particularly in the last decade, writers have been recognizing the truth which Von Pirquet saw concerning the fundamental oneness of immunity and sensitivity reactions, and concerning the role of bacteria in allergy.

Burky,[3] Kabat,[9] Wittich,[14] Doerr,[1] Baer,[1] and others have favored this view. Harrington[5] suggests that "anaphylaxis and allergy appear as an embarrassing variant of the same mechanism," and William C. Boyd[2] recently wrote as follows, "Bacterial disease agents seem to act in one or both of two ways: to lead to the formation of protective antibodies or to produce in the host hypersensitivity or allergy to some constituents of the bacterial cell."

Should Von Pirquet's original allergy be subdivided today into immunity reactions, or normalergy, and sensitivity reactions, or exaggergy?

Perhaps all cases of sinusitis are allergic in the Von Pirquet sense, the symptoms and signs in a given case depending upon the proportions which exist between the two types of reaction. The cytologic findings which are usually recorded *could* be interpreted as favoring this viewpoint; increased eosinophilia representing a tendency towards sensitivity reaction, and increased neutrophilia showing more immunological response—both types of cells being usually present to some extent. Hitherto those cases where the immunity response has resulted in marked local symptoms, usually with pus present, or structural changes which can be shown by x-ray, have been called infective sinusitis by the eye, ear, nose and throat surgeons. When local symptoms have been predominantly of the noninflammatory type, the condition has been called allergic sinusitis, and a search usually made for a nonbacterial allergen. Attention has usually been paid to attempts to remove the results of reaction surgically. or to avoid the nonbacterial allergen. Attempts to increase the degree of immunological reaction, or to reduce the sensitivity reaction, have apparently been more successful with some substances than with others.

In pollenosis the nonviable allergen is fairly obvious, a suitable extract can be made, and ascending doses to an optimum size will often so alter the reaction of the body as to relieve the most embarrassing symptoms. Just how is this result accomplished in the body? Why is it not always so accomplished? While we have some theories, we do not know; but our failure to know the "how" is not a reason to refrain from using a treatment which relieves many hay-fever victims!

What about other allergens? Much work has been done with "house dust," another way of saying something or some things which settle as precipitate matter from the air of rooms in which people live. Could the major allergen in house dust be bacteria? The following considerations favor such an idea:

1. Ordinary dust contains many bacteria. Deryl Hart[6] and associates have shown that when healthy masked people occupy an apparently sterile operating room "the air in the operating room is highly contaminated with pathogenic bacteria." Others have corroborated this finding. How much more will the accumulated dust of days in living rooms, whose inhabitants are not masked, contain bacteria? This truth has been studied by Hollaender[7] and associates, Wells and Wells,[13] Thomas,[10] and Murray P. Howard,[8] mostly in connection with infections causing immunity-type reactions in surgical conditions or contagious diseases. Their work has proved that one of the largest elements in household dust is bacteria, especially streptococci and staphylococci.

2. Bacteria represent practically the only allergen which increases in quantity after reaching the body. A few bacteria will very soon multiply in the warm moist linings of the respiratory tract—living allergen, which by the amazing alchemy of the life force is able to use the materials of the host's body to make many thousand times as much allergenic material as was introduced originally!

3. There is evidence to show that dust from such materials as cotton, wool, et cetera, which has "aged" where people live is much more likely to be allergenic than that coming from new materials. This could be because of the bacterial materials which they have accumulated in the course of "aging."

4. In a very few cases where there was a positive skin reaction to "house dust extract" the writer injected about 1/50 c.c. of a mixed (non-sensitized) respiratory vaccine intradermally. This resulted in a wheal very similar to that produced by the dust extract. These few cases are no more than suggestive. Perhaps someone with better facilities will undertake more investigation along these lines. While skin tests do not prove anything in an absolute or dogmatic sense, it would be interesting to know whether a large percentage of those whose skins are sensitive to house dust extract are also similarly sensitive to dead bacteria.†

5. A number of workers who consider they get good results with house dust extracts in treatment frequently add bacterial vaccines to the extract.[12] Moreover, since dry dust contains 20 to 70 per cent organic matter,[8] any extract will of necessity be a form of foreign protein therapy.

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†Preceding this paper, one was presented to the American College of Allergists on the work of Doctors Kraft, Mothersill, and Nestman, of Indianapolis, showing that about *30* per cent of their subjects gave immediate urticarial reactions to intradermal injections of bacterial antigens. In personal conversation with two of the authors the present writer learns that their figures were very conservative; had they reported all their *slight* reactions the figure would have been more like *65* per cent.

6. Respiratory allergies seem to be benefited by treatment with sensitized vaccines, properly given, with at least as much success as if treated with house dust extract, even in cases where skin tests are positive to dust extract.

The use of bacterial vaccine is, of course, an attempt to alter the type of reaction of the host—to increase his immunity, or decrease his sensitivity, or both, either specifically or nonspecifically. There have been many contradictory reports as to successes and failures in such attempts.

While there are various references to the use of sensitized vaccines in respiratory infections, the writer has been able to find none to their use in the comparatively large doses he has been using routinely for many years. The sensitizing process is reported by the makers to consist of treating the bacteria with hyperimmune rabbit serum before they are killed. The cells are supposed to take up specific antibodies by adsorption. All serum is removed and the ultimate product is a saline suspension of the "sensitized" bacterial cells.

In the author's cases there has been some evidence of specificity, e.g., a very severe case of sinusitis which improved on a mixed sensitized vaccine continued to give much distress until it was found that pneumococcal infection was involved. Administration of additional pneumococcal antigen cleared up the condition completely. There is also evidence of a nonspecific effect. A few cases of hay fever of the early summer type who came too late to be given grass pollen extract, got such marked benefit from a few "shots" of sensitized mixed vaccine that they went through the summer without symptoms. This is consistent with the evidence given by the late Sir Almroth Wright,[15] who considered that nonspecific immunization is elaborated by the leukocytes.

Possibly some of the benefit obtained from vaccine is of another nonspecific type. If the congestion due to reaction against bacteria is relieved by a reduction of the number of bacteria, because of an increased specific immunity, this would result in a decreased absorption of nonviable allergens, and a consequent lessening of the sensitivity reaction.

Anyone wishing to test the value of this treatment must observe three fundamentals:

1. An efficient antigen must be used. The sensitized product* seems to be efficient.
2. It must be injected subcutaneously—not intramuscularly.
3. The dosage must be sufficient.

Many commercial vaccine manufacturers recommend a maximum dose of 200 million of each organism or perhaps 800 million of all organisms.

Even the makers of the sensitized vaccine* recommend maximum doses

*H. influenzae Serobacterin Vaccine Mixed. Manufactured by Sharp and Dohme Incorporated. Philadelphia, and said to be made from sensitized killed *H. influenzae*, *N. catarrhalis*, *K. pneumoniae*, of each 500 million; D. pneumoniae (types 1, 2, 3, 4, 5, 6, 7, 8, 14), 2,500 million; Staphylococcus aureus and albus, of each 750 million; Streptococcus (hemolytic, group A, types 1, 3, 5, 6, 12, 17, 18, 19), 1,500 million; totaling 7,000 million organisms per c.c.

only of the order of 500 to 2,500 million individual organisms and 7,000 million total count.

For many years the writer has been using maximum doses equivalent to 17,000 million of all organisms. *Many patients do not show improvement until receiving doses of that magnitude!*

Even these doses have sometimes had to be increased slightly to get results. It is no wonder some patients do not acquire sufficient immunity or hyposensitization from doses 1/20 to 1/15 these amounts!

In the present state of our knowledge, one would not dare to dogmatize as to how the body's reaction is changed by this vaccine therapy, but our ignorance is no reason not to secure the benefits. The use of vaccine is not a reason for neglecting any other useful procedures; nor is any other treatment a reason not to use vaccine. For example, polyps and other neoplasms require appropriate treatment, but patients with polyps and those who have had polyps removed will be detoxicated and "feel better" after a course of sensitized vaccine. Pollenosis requires specific desensitization, but vaccine therapy will often remove an added source of irritation. Penicillin inhibits development of many bacteria frequently found in sinusitis, whereas sensitized vaccine increases the effectiveness of the body's immunologic mechanism. The two methods of treatment are complementary.

Drainage from the sinuses is probably aided by using 1 per cent ephedrine in normal saline, or ¼ per cent Neosynephrine, et cetera, by a postural method—but not oftener than twice in twenty-four hours for fear a compensatory congestion may result.

The writer thinks of sensitized vaccine not as a cure-all for sinusitis but as a most useful product. He has learned some principles for its use. which are offered herewith in somewhat dogmatic form:

Product.—H. influenza Serobacterin Vaccine Mixed (No. 4750). Sharp and Dohme.

Interval Between Doses.—As short as three days between smaller doses and five to seven days between larger doses. Doses should not be repeated or increased at intervals of over one month.

Give Subcutaneously.—Not intramuscularly. It is often advisable to divide doses of over 1 c.c., giving half in each of two places.

Local Reactions.—Usually a reddened area about the size of a quarter and some tenderness. If an area of several inches diameter or excessive muscular soreness occurs, it is advisable to repeat the last dose before proceeding to increase dosage.

General Reactions.—These are rare, but a *slight* one is often very beneficial. When chilliness and a feeling for a few hours of taking the "flu" occur, it is well to repeat the last dose or slightly reduce it before proceeding to increase dosage.

In the vast majority of cases one can give the following doses at intervals suggested with very little inconvenience to the patient. These doses can be given to infants and small children safely.

0.2 c.c.; 0.4 c.c.; 0.8 c.c.; 1.2 c.c.; 1.8 c.c.; 2.5 c.c.

In resistant cases repeat the 2.5 c.c. dose several times at intervals of *one to four weeks.* In a few cases, doses of 3 c.c. have to be given before securing an optimal result.

It is naturally a good idea to make sure that the patient's vitamin intake is adequate. It is possibly fair to say that while vitamins will not confer immunity, it is difficult or impossible for the body to develop immunity without an adequate supply of vitamins.

SUMMARY

A sensitized mixed vaccine, injected subcutaneously in sufficient dosage, accompanied by medical drainage, has resulted in relief of symptoms for hundreds of patients with sinusitis treated during a period of over twenty years.

The following considerations may aid in understanding this phenomenon:

1. All sinusitis is possibly allergic in the Von Pirquet sense, and there is not necessarily any sharp line of division between sensitivity and immunity. They may occur together.
2. The great group of persons who are "allergic to dust" may be merely sensitive to bacteria.
3. It is possible that in addition to any specific immunity or hyposensitization, there is also a nonspecific effect which is sufficient to cause the patient to lose his sensitivity to various foreign substances.
4. Increase of specific immunity presumably causes a decrease in the congestion present by reducing the bacterial insult. This should result in reduced absorption of other allergenic material.

REFERENCES

1. Baer, Rudolf L., and Leider, Morris: Dermatologic allergy. Ann. Allergy, 5:578-93, (Nov.-Dec.) 1947.
2. Boyd, William C.: Immunochemistry. J. Allergy, 18:125-45, (March) 1947.
3. Burky: As quoted in "The physiologic and immunologic aspects of allergy" by Dr. Fred W. Wittich, 1944 Regional Course (Course No. 2), American College of Allergists.
4. Doerr, Robert B.: Allergic phenomena. Ann. Allergy, 4:339-49, (Sept.-Oct.) 1946.
5. Harrington, C. R.: Brit. M. J., 28, (Jan. 4) 1947.
6. Hart, Deryl.: Sterilization of the air in the operating room by bactericidal radiant energy. Arch. Surg., 37:956-72, (Dec.) 1938.
7. Hollaender, A., DuBuy, H. G., Ingraham, H. S., and Wheeler, S. M.: Science, 99:130-31, (Feb. 11) 1944.
8. Howard, Murray P.: The bacteriology of household dust. J. Bact., 21:14-17, 1931.
9. Kabat: As quoted in "Clinical and comparative allergy" by A. J. Weil. Ann. Allergy, 5:42-46, (Jan.-Feb.) 1947.
10. Thomas, John C.: Reduction of dust-borne bacteria by oiling floors. Lancet, 2:123-127, (Aug. 2) 1941.
11. Von Pirquet, C.: Allergic. Ann. Allergy, 4:388-90, (Sept.-Oct.) 1946.
12. Waldbott, George L.: Does the routine treatment of asthma need revision? Ann. Allergy, 5:126-31, (March-April) 1947.
13. Wells, W. F., and Wells, M. W.: Air-borne infections. J.A.M.A., 107:1698-1703, (Nov. 21) 1936; and 107:1805-09, (Nov. 28) 1936.
14. Wittich, Fred W.: The physiologic and immunologic aspects of allergy. 1944 Regional Course (Course No. 2), American College of Allergists.
15. Wright, Sir Almroth: Studies on Immunization. Second series. Pp. 194, 246 London: William Heinemann Medical Books Ltd., 1944.

"CEREBRAL EDEMA" DUE TO PHENOBARBITAL SENSITIVITY

Clinical Study of a Case

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THE study of the influence of allergy on the brain was limited indeed until Vaughan,[13] in 1927, demonstrated and reported that migraine in many instances was a manifestation of allergy.

The attention of the allergist and internist has been centered largely on the cutaneous response to drug allergy, chiefly because few such cases reach the autopsy table for gross examination of organs and subsequent microscopic examination of tissues. This is particularly true for phenobarbital sensitivity, as only two cases of phenobarbital eruptions with a fatal outcome[6,9] were reported up to 1941. During that year Winer and Baer[14] reported a third case with a detailed clinical and post-mortem study. Necropsies were obtained in two of these cases, but no mention was made of examination of brain tissue.

Every type of skin manifestation may be evoked by drugs, and the same drug may elicit the most varied responses in the same patient.[12] In fact, drug reactions may simulate any allergic response of any type, affecting any of the organs of the body,[1] and sensitivity may occur by one route and exacerbation by another route.[2]

Not infrequently, headache is one of the symptoms of drug allergy. Kennedy[7] states that the allergic headache has not received nearly enough attention and that many cases of sudden transient cerebral and spinal illnesses can only be explained as being due to a sensitiveness of an allergic character.

The patient described in this report presented cerebral manifestations not frequently observed and multiform cutaneous responses, following exposure to phenobarbital.

CASE REPORT

Miss O. G., a nurse, aged twenty-one years, was admitted to the hospital at 11:30 a.m., February 4, 1946, in a semicomatose condition of two hours' duration. Breathing was markedly irregular. She presented a multiform rash, predominantly morbilliform on the face, neck and extremities, with areas of urticaria and angioneurotic edema.

The history of this illness had to be obtained from her roommate because of the patient's stuporous condition and incoherent speech.

The present illness began approximately five hours before hospitalization, at which time the patient complained of generalized pruritus, rash, and urticaria, with progressive swelling of the eyelids and lips, dull headache and slight fever. She had sought relief from pruritus by means of oatmeal baths without apparent benefit. Further questioning of her friends on the afternoon of admission elicited information that three weeks prior to the present illness the patient took a sulfadiazine tablet (gr. 7.7) four times a day and a phenobarbital (Luminal) tablet (gr. 1½) at bedtime

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for five days, for a "head cold," with complete subsidence of nasal discharge. She continued at her routine duties as a nurse in a contagious disease unit of a large hospital but complained frequently to her roommate of easy fatigue and insomnia at night. Because of further progression of the rash, urticaria, angioneurotic edema and pruritus, hospitalization was advised.

Physical Examination.—The patient was a well-developed and fairly well-nourished young woman in a semicomatose state, acutely ill with morbilliform eruptions of the face, neck, arms and legs, and with scattered scarlatiniform lesions and a few areas of erythema multiform-like lesions most evident on the upper chest, flexor surfaces of the arms, and inner aspects of the thighs. Many urticarial wheals were present on the face, neck and extremities, with marked edema of the lips and eyelids extending over the cheeks.

The forearms, medial surfaces of the thighs, neck and upper portions of the back presented linear excoriations, apparently made by the patient's fingernails on scratching. On admission her temperature was 99.8° F., pulse 76. Respiration was irregular with varying periods of hyperpnea and apnea. The blood pressure was 124/86.

The pharyngeal mucosa was normal in appearance, and indirect laryngoscopy revealed laryngeal structures of normal appearance with no evidence of obstruction. Ascultation and percussion revealed no abnormalities of the thorax, heart or abdomen, with the exception of the irregular breathing previously mentioned. The pelvis was essentially normal.

Many possible clinical diagnoses were entertained at first, namely, measles, rubella, erysipelas, scarlet fever, toxic drug reaction, and drug allergy. The acute infectious diseases were considered because of the skin manifestations, elevation of temperature and a history of recent exposure in a contagious disease unit during her nursing assignment. However, an indirect history of recent phenobarbital ingestion prompted the immediate consideration of barbiturate poisoning.

Picrotoxin 1 c.c. (3.0 mg.) was given intravenously for two doses at five-minute intervals, followed within fifteen minutes by metrazol 3 c.c. (0.3 gm.), but with no discernable improvement.

Four hours later the patient became very irritable, restless and difficult to restrain in bed, with an accentuation of the respiratory irregularity. Phenobarbital sodium (Luminal Sodium) gr. 1½ was given subcutaneously. Within forty minutes the patient was in deep coma with Cheyne-Stokes respiration and an increase in urticarial lesions, followed one hour later by an increase in blood pressure (140/90) and temperature (101.2° F.), with two vomiting attacks.

Phenobarbital sensitivity was then suspected, with probable cerebral disturbance. Ophthalmoscopic examination was requested, which revealed an elevation of the disc, blurring of the margins, dilatation and tortuosity of the vessels and edema of the retina. A spinal puncture was done with the patient in the horizontal position, and the fluid reached a level of 340 mm. in the water manometer. Ten c.c. of macroscopically clear fluid were removed with no evidence of xanthochromia or turbidity. No pellicle was observed on standing.

Laboratory Findings.—Blood: red blood cells, 4,700,000; white blood cells, 4,800; hemoglobin, 13.8. Differential count: polymorphonuclear cells, 68; lymphocytes, 27; eosinophiles, 4; monocytes, 1. Kahn test, negative; Wasserman test, negative. Sedimentation rate, 11 mm. in 60 minutes.

Urine analysis: reaction, acid; specific gravity, 1.024; reducing sugar, negative; albumin, trace.

Spinal fluid: pressure, 340 mm. water (normal 110-130 mm. Ringer's solution, in recumbent position); color, clear; protein, 32 mg. per cent (normal 16-38 mg. per

cent); sugar, 70 mg. per cent (normal 45-80 mg. per cent); cells, 6 lymphocytes and no polymorphonuclear cells (normal 0-5 lymphocytes per cubic mm.); chlorides, NaCl 740 mg. per cent (normal 720-750 mg. per cent).

(The normal findings of the cerebrospinal fluid are from Best and Taylor: Physiological Basis of Medical Practice, 4th ed. Baltimore: Williams and Wilkins Co., 1945.)

Therapy.—Venous infusions of 50 c.c. of 50 per cent glucose were given at one-hour intervals, for two successive injections, in an effort to reduce intracranial pressure. Epinephrine hydrochloride, 1:1000, minims 6, was given subcutaneously at thirty-minute intervals, for six injections, followed by a copious diuresis. The urticarial lesions began to recede with a concomitant reduction in the edema of the eyelids, lips and face.

A second spinal puncture was performed eight hours after the first, and approximately 12 c.c. of clear fluid was withdrawn. No manometric reading was made, but the fluid spurted for a distance of 5 to 6 inches, indicating that it was still under pressure. The characteristics macroscopically were the same as those of the first specimen. The patient became less comatose and within one hour and a half complained of a dull headache at the base of the skull, which disappeared approximately four hours later.

Daily infusions of hypertonic glucose (500 c.c., 10 per cent) were given for four days, and favorable results followed this therapeutic regime, with marked clinical improvement within forty-eight hours. She became relatively lucid and gave the information that during the night prior to hospitalization she had ingested a phenobarbital tablet (Luminal) gr. 1½ at bedtime because of insomnia and fatigue. During this interval she denied taking any other medication. A past history was obtained from the patient for the first time during this period of questioning.

Past History.—She had frequent colds three to four times a year, not seasonally, and a sore throat three to four times a year. She was a known streptococci carrier (Beta hemolytic type) but usually responded to sulfonamide therapy. She denied hay fever, bronchial asthma, eczema and sinusitis. Her surgical history was negative. She had had immunizations for smallpox, diphtheria, and whooping cough, with no known sequelae.

Her allergic history revealed frequent abdominal bloating with cramps, a scarlatiniform rash and urticaria, followed by a headache, after eating cranberries and strawberries. Her family history was negative for asthma, hay fever, migraine, tuberculosis, allergic rhinitis, sinusitis, eczema and urticaria.

The clinical course of the patient showed satisfactory progress with the aforementioned therapy, and on the fifth hospital day she was well oriented, sitting in a chair, with a normal temperature, pulse, respiration and blood pressure (120/82). Food was given by mouth without postprandial distress, and a hospital discharge was considered. It was suggested at this time, however, that cutaneous tests be made with phenobarbital, realizing fully that only in exceptional instances and only occasionally in true urticarial drug eruptions will the appropriate skin test prove valuable.[11] The test was performed and revealed a 1-plus to 2-plus reaction (wheal 0.5 cm., with moderate areola). Similar tests were made later with Seconal Sodium and Sodium Amytal with no reaction.

One hour after the test with phenobarbital, the patient was semicomatose, with irregular respiration and with alternate periods of hyperpnea and apnea. The temperature rose to 99.8° F., and the skin manifestations simulated those of the day of admission.

A venoclysis of hypertonic glucose with epinephrine was employed. The cerebral and respiratory symptoms disappeared within six hours. A slight pigmentation of the skin in the areas of previous urticaria persisted for days.

In our effort to procure an additional confirmatory diagnostic aid, we employed the passive transfer test six days after the direct skin test, and the response was similar to the cutaneous test, though with slightly less erythema. Occasionally a passive transfer is temporarily positive in drug allergies, as shown in a case of Criep[3] and of Zeller.[15].

The remainder of the hospital stay was uneventful, and the patient was discharged symptom-free on the fourteenth hospital day, with the advice to avoid drugs containing phenobarbital. Such avoidance has led to freedom from symptoms.

SUMMARY AND CONCLUSIONS

1. A case of multiform cutaneous lesions with fever, urticaria, angioneurotic edema, coma and marked increase in cerebrospinal fluid pressure after phenobarbital exposure, is reported for the first time.

2. The antigen in this case is most likely a hapten,[8] a drug-protein combination resulting from a conjugation with one of the plasma or tissue protein fractions. It appears, however, that the chemical substance itself may react with the antibodies once they are formed.[10]

3. Drug sensitivity, as represented by this case, often develops in patients who have taken a drug without reaction for months or even years, yet, subsequently, experience a severe, almost fatal reaction following the exhibition of an amount much smaller than the recommended therapeutic dose.

4. A high index of suspicion of drug sensitivity should exist in any atypical condition where there is a history of exposure to the drug. Usually these drugs are for headache, pain, insomnia or constipation.

5. Next to aspirin, the group of barbituric acid compounds is probably the most widely employed of the drugs in general use.[5] This is particularly true for persons engaged in medicine and allied fields, because of frequent fatigue, insomnia and the ready availability of the drug.

6. Many allergic conditions, because of reversibility, may not be diagnosed if the history, signs and symptoms are not properly evaluated early; and although positive skin tests will not often be successful, there should be no abandonment of all forms of skin testing in suspected drug allergy.[4]

7. The clinical signs and symptoms in the case reported, with the ophthalmoscopic findings and marked increase in cerebrospinal fluid pressure, are indicative of cerebral edema with increased intracranial pressure. These recurred with a similar clinical course after re-exposure to the suspected drug. These findings, I believe, substantiate the diagnosis.

I am grateful to the Departments of Ophthalmology and Otolaryngology, Provident Hospital, for assistance in the work-up of this case. I also wish to acknowledge particularly the co-operation of Dr. J. M. Richardson in the ophthalmoscopic examinations and Dr. Harold Wagner, Billings Hospital, for suggested therapy.

REFERENCES

1. Brown, E. A.: Drug allergy. Fall Graduate Instructional Course, American College of Allergists, Chicago, 1944.
2. Brown, E. A.: Allergy to drugs and antibiotics. Fall Graduate Instructional Course, American College of Allergists, Cincinnati, 1947.

(Continued on Page 396)

BACTERIAL ALLERGY

An Extreme Hypersensitization Commonly Found in Chronic Brucellosis

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IT is well known that some invading bacteria have a greater capacity for producing a hypersensitive state than others. For example, the tubercle bacillus produces in many patients a marked hypersensitiveness to its specific proteins. This is the basis of the local tuberculin reaction of the cutaneous diagnostic tests of Von Pirquet, Wolff-Eisner, Moro, Mantoux and Vollmer, and of the focal and general reactions following subcutaneous injection of tuberculin which have made tuberculin therapy in pulmonary tuberculosis difficult and hazardous. The causative organisms of rheumatic fever and perhaps rheumatoid arthritis are thought by many[12] to be relatively benign unless and until the host begins to produce a hypersensitive collagenous reaction in the connective tissues, usually some weeks or months after the onset and subsidence of the acute invasion.

Less well known is the fact that extreme sensitization to substances of Brucella organisms occurs very readily in brucellosis (undulant fever) and that this sensitization is a common cause of chronic illness.[13,14] At least 10 per cent of the general population have become sensitized to Brucella, as determined by skin-testing surveys.[1,2,9,11] This figure is much lower in eastern urban areas where pasteurization of the milk supply has been practiced for many years. It is very much higher in areas where raw milk has been customarily consumed.[7] It is also higher by 50 per cent in groups of patients who present diagnostic problems associated with chronic illness, debility and rheumatoid and psychosomatic symptoms.[4]

When a patient who is chronically or recurrently ill presents any clinical and laboratory evidences of Brucella infection, such as fever hyperidrosis, typical blood counts and positive blood agglutination, opsonic, or complement fixation reactions, a diagnosis of chronic brucellosis is usually made. In our experience with about 500 cases of chronic brucellosis, the incidence of detectable skin sensitivity to specific Brucella substances has been 98 per cent. Other writers[4,16,17] state that the skin tests may be negative in 5 to 10 per cent of cases of chronic brucellosis. The diagnosis is often so difficult to prove that it seems hazardous to diagnose chronic brucellosis in the face of negative skin tests unless a positive Brucella culture or other strong evidence is obtained. It is well known that many persons who are apparently perfectly healthy also react to Brucella substances with positive skin tests,[18,20] so a diagnosis on this basis alone is often not tenable.

The extreme degrees of hypersensitization (Fig. 1) to Brucella, consisting of complete tissue intolerance to ordinary doses of Brucella proteins,

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resulting in necrosis of the skin, indolent ulcer formation and permanent scars, have been found to occur, in our experience, only among patients with chronic brucellosis. These reactions differ markedly from the ordinary large positive skin reaction, consisting of temporary indurated erythema

Fig. 1. The left arm presents a reaction to brucellergen which was positive but was considered inconclusive. Five days later a skin test with undiluted vaccine was given on the right arm. The photograph shows the resulting necrosis as it appeared three weeks later.

of a few weeks' or months' duration and commonly called 3 plus or 4 plus, which may be encountered in veterinarians and other cattle-and-pig handlers who are not sick. If Brucella vaccine is injected subcutaneously into the extremely hypersensitized patients with chronic brucellosis, it produces liquefaction necrosis and sterile abscesses at the sites of injection (Fig. 2) as in the Arthus phenomenon. Patients afflicted with such a degree of hypersensitiveness to Brucella will react in this manner quite uniformly to any ordinary doses of vaccine or Brucella skin testing materials. We have never seen a patient with such a reaction who does not have chronic and recurrent complaints which are incompatible with good health and which are typical of chronic brucellosis. The incidence of the extreme type of brucellar hypersensitization has varied between 16 per cent and 25 per cent in groups of 100 patients with chronic brucellosis, according to our records. If, in the future, as a result of improved methods of diagnosis, chronic brucellosis should be proved to be more common, this incidence of hypersensitization will prove to be proportionately too high. On the basis of these figures, extreme brucellar hypersensitiveness is a serious obstacle to the successful treatment[14] of one patient out of every five who are recognized as having chronic brucellosis.

In practice, extreme hypersensitization assumes an even greater importance in treatment than is indicated by the above figures. The methods of vaccine therapy which have usually been advised for chronic brucellosis have called for large doses equivalent to several hundred thousand or several million killed bacteria. Apparently the objective has been to shock or jolt the patient into resisting the disease. Unfortunately, this procedure,

when done with Brucella substances, often increases the patient's sensitization, instead of, or in addition to, immunizing him. As a result of such sensitizing treatment, the patient remains ill, sometimes even worse than before treatment, in spite of the presence of a reassuring titer of opsonins and agglutinins in his blood stream. If large doses of vaccine are continued and are given too frequently or too infrequently, many patients show an increasing intolerance to the vaccine, both locally and generally, even though no excessive hypersensitivity to Brucella was present at the time of the diagnostic skin test (Fig. 3). Such a patient is becoming sensitized and vaccine therapy will have to be discontinued, usually without a cure or even much improvement. In our experience with large doses of unmodified Brucella vaccines, only 60 per cent of the patients improved,[14] a percentage too low to justify such unpleasant treatment. Consequently, Brucella vaccine therapy has been abandoned by many physicians who have had similar experience.

The following cases illustrate the above points:

Case 1.—Mrs. A. B., aged forty-five, had suffered from chronic brucellosis which went undiagnosed for at least five, probably ten years. Her chief symptoms had been lack of energy, myalgia, headaches, severe eyestrain without refractive error, eczema, twitching of the eyelid, occasional tachycardia, and severe constipation. Extensive treatment for allergy resulted in only slight success. There was no eosinophilia. Her Brucella agglutination reaction was negative, but her phagocytic index number (Foshay) was 65 per cent. After the blood was taken for these tests she was given 0.10 c.c. of Brucellergen 1:12,000 intracutaneously on the right forearm. This resulted in a necrotic ulceration, 1 cm. in diameter, at the site of injection. At the same time a herpetiform lesion appeared on the right forefinger and the patient was seized by a severe lassitude and somnolence. In order to determine the specificity of this necrotic reaction, the patient's allergist skin-tested her to nucleic acid, phenol and salt, which are the only ingredients in Brucellergen other than the specific Brucella proteins. These tests were negative, proving that the Brucella proteins were responsible for the reaction. Ten subcutaneous injections of oxidized Brucella vaccine in doses representing material of from two million down to 0.4 of one bacterium, all produced persistent red nodules topped by slight superficial necrosis of the epidermis. During this time there was no clinical improvement and the eczema became worse. After one month without vaccine, the patient was given a dose of 0.05 c.c. of a 10^{-12} dilution of the vaccine intravenously. Theoretically, this represented the protein from 0.00002 of one Brucella bacterium. It put the patient to bed for one and a half days with headache, fever of 2 degrees and inability to sleep. Four more intravenous doses were tolerated with much less general reaction, but when intramuscular doses of the same size were attempted again, necrosis of the needle tracts recurred and desquamation continued at these sites for three months.

Case 2.—H. N. H., a nurse, aged forty-six, had had, from 1934 to 1938, encephalitis, optic neuritis, cholecystitis, and osteomyelitis of the upper jaw, resulting in a permanent draining fistula. In 1938 the case was diagnosed as brucellosis by Dr. W. H. Gaub, and the patient was given treatment by intracutaneous injections of Brucella vaccine. Each injection resulted in a large slough. Four years later she presented herself with seven smooth depressed scars in her skin, 2.5 to 9 cm. in

diameter. She had been disabled for six years. After failing to respond to two other kinds of vaccine, she was rehabilitated by extremely careful desensitization with Foshay's oxidized Brucella vaccine. She was never cured. Her sister and her sister's daughter also had chronic brucellar osteitis and hypersensitization.

Fig. 2.

Fig. 3.

Fig. 2. The patient's left upper arm presents sterile abscesses and depressed scars of healed subcutaneous necrosis caused by each of six doses of commercial Brucella vaccine.

Fig. 3. Some of the thirty red, indurated sites of intracutaneous and subcutaneous injections of commercial Brucella vaccine presented by a patient with chronic brucellosis of three years' duration. Fifteen sterile abscesses and granulomas were excised from this patient before desensitization could be started.

Case 3.—A. V. S., a physician, aged sixty-nine, had an insidious onset of a gradually disabling illness which he correctly diagnosed as undulant fever. He had been drinking and prescribing raw milk. His agglutination test was negative. He was given 0.10 c.c. of Brucellergen 1:12,000 intracutaneously. A 4-plus reaction with slight central softening and premature desquamation resulted. He was given 0.25 c.c. (500 million killed bacteria) of a commercial Brucella abortus and Brucella suis vaccine, as advised on the leaflet accompanying the vaccine. The dose was repeated once and then doubled. The patient experienced such an exacerbation of aching, depression, and somnolence after each injection that this vaccine was discontinued. He developed a painful glossitis, multiple ulcerations of the pharynx, diplopia, marked torpidity, occasional short deleria, loss of memory, complete aversion to food and generalized stiffness of muscles and joints. A sterile abscess was formed at each of the three sites of vaccine injection. The abscesses were evacuated of liquefied fat and pus which, on culture, were found to be sterile. These necrotic reactions appeared very slowly over a period of two to six months. The lesions did not heal for seven months. Meanwhile, every possible attempt to desensitize the patient or to improve his condition resulted in failure. He reacted generally to an intravenous injection of the protein of only four bacteria. He showed no improvement until after the last abscess had entirely healed, after he had spent seven months in bed. He was disabled for one year, and he has never fully recovered.

Case 4.—F. J., aged thirty-four, presented herself with two scars from necrotic skin reactions to Brucella substances given five years and three years previously. In addition, she had large scars from sterile abscesses on both upper arms and on one thigh and one persistent nodular induration which had been present for three years in the subcutaneous areolar tissues. These resulted from commercial vaccine which had been started within two days after the second skin test was given. This unfortunate experience with vaccine could have been avoided if the significance

of the first necrotic skin test had been fully appreciated. This patient, like many other such hypersensitive cases, has a lesion in her spine, which is typical of brucellar spondylitis.[5,15,19,25]

The cases cited above are representative of at least fifty such cases seen by us during the past ten years. They illustrate the objective manifestations of extreme brucellar hypersensitization; and that sensitivity increases whenever the reaction is severe enough to result in tissue breakdown, and that desensitization is practically impossible as long as such necrosis continues unhealed.

THE SPECIFICITY OF HYPERSENSITIVENESS IN BRUCELLOSIS

Many patients with chronic brucellosis have had symptoms which have led to a diagnosis of allergy, as in Case 1 above. Nasal catarrh, allergic "sinusitis," frequent sore throat, persistent cough, migrainoid headache, easy fatigability, skin eruptions and myriad gastrointestinal disorders are all common in chronic brucellosis. Patients with these symptoms usually do not respond to treatment for food and pollen allergies, as in Case 1 and many others. The question arises, are these symptoms due to active invasion of the involved tissues by living Brucella organisms or are they merely local tissue manifestations of a generalized hypersensitive state due to foci of brucellar antigens elsewhere in the body, or are they due to extrinsic allergens to which the body reacts excessively because it is already fighting a chronic infectious disease and is therefore in a nonspecifically hypersensitized phase? Fondé[6] seems to conceive of a combination of the last two explanations. Certainly our experience enables us to agree that hyposensitizing patients with chronic brucellosis by means of dilute Brucella vaccine brings about more improvement of all their symptoms than can be expected from any other therapy.

Although acute brucellosis is accompanied by invasion of practically all body tissues[21] by Brucella organisms with the formation of granulomata,[22,24] and although we know that most strains of Brucella prefer an intracellular existence,[3,10] we lack cultural evidence that the respiratory and gastrointestinal symptoms of chronic brucellosis are due to the presence of living Brucella organisms in the reacting tissues. Whether residual antigen may continue to remain in the tissue cells after the microorganism has died is not known. The clinical picture in many cases of chronic brucellosis suggests that hypersensitive reactions do take place in many tissues of the body where active infection cannot objectively be proved.

As for extrinsic allergens, we have seen cases of brucellosis in which they were responsible for important complications. But we have seen more cases in which the patients were tested and found insensitive to extrinsic allergens. Case 4, for example, has been studied extensively in many of the diagnostic clinics of this country by various methods, and no extrinsic allergen has ever been detected. Yet this patient is the most severely

sensitized person, as far as Brucella is concerned, we have encountered. It is chiefly the evidence growing out of the quantitative study of Brucella hypersensitization that inclines us to believe that hypersensitiveness in chronic brucellosis is highly and chiefly specific.

QUANTITATIVE STUDIES OF HYPERSENSITIVITY

Our good results in treating those patients with chronic brucellosis who are not extremely hypersensitive with oxidized[8,14] Brucella vaccine led us to attempt to hyposensitize the group of extremely hypersensitized patients also. The first task was to find out how small the dose of vaccine must be in order to be tolerated by the most hypersensitive patients. The vaccine was diluted progressively as the need arose until 12 decimal dilutions were reached. Since this approached the theoretical limit of dilution for protein molecules, it seemed unreasonable to dilute further. However, further dilution was demanded by the persistence of tissue intolerance at this level of dosage. Apparently flying in the face of theory, we diluted to 20 decimal dilutions: that is, we took a vaccine suspension containing about 400,000,000 bacteria per c.c., killed and oxidized, and diluted it with physiological saline by 10^{20} Phenol, 0.2 per cent, was added to the diluent as a preservative. Control injections of the diluent and the phenolized diluent which were frequently given to our patients elicited no reactions. The dilutions were frequently cultured, and none were found to be contaminated. Theoretically, the ninth dilution would be the last one to contain the amount of protein in one bacterium. Protein molecules would be expected to disappear at about the fourteenth dilution. In the twentieth dilution it is hard to see how any of the original substance could still be present. Nevertheless, there were more than a score of patients *who could not tolerate doses of the twentieth dilution without objective* local reactions lasting for more than two weeks, and subjective general reactions which were too uniform to be doubted.

Physical chemists were consulted, and it was agreed that Brucella proteins were probably being adsorbed on syringes, needles, bottles, et cetera, in spite of meticulous cleaning methods. It was assumed that the adsorbed proteins from strong dilutions contaminated the weaker dilutions in unpredictable quantities, thus giving rise to the hypersensitive reactions in the hypersensitized patients. We know two physicians who, unaware of this error, diluted Brucella vaccine empirically and progressively until they were using 120 and 750 decimal dilutions respectively! Because they were not removing all of the vaccine from their syringes and needles in their cleaning processes, they continued to get objective reactions to these infinite dilutions, which were indefensible on theoretical and mathematical grounds. Their clinical results were also quite good, though inconsistent, because minute traces of vaccine were actually present in unknown doses of molecular size.

To eliminate the error of adsorption,[26] new dilutions were made up using

dilution. The upper site was caused by 0.05 c.c. of the eighteenth dilution and is proportionately larger. The reactions did not disappear for one month or more. There was necrosis of the superficial layers of skin around the needle tract of the eighteenth dilution. The reaction to a control injection of the diluent given below these three sites was negative. The photograph was taken forty-eight hours after the injections were made.

SUMMARY AND CONCLUSIONS

It is clear that our quantitative study of brucellar hypersensitization is far from complete. Phenomena have been observed for which we now have no theoretical explanation. The clinical significance of our findings to date, however, can be summarized as follows:

1. Regardless of the ultimate explanation of the activity of the extreme dilutions of Brucella vaccine, the fact appears established that some patients with chronic brucellosis develop very severe degrees of hypersensitization to Brucella vaccine.

2. Tissue necrosis resulting from hypersensitive reaction seems to increase hypersensitization and to prevent hyposensitizing procedures until after healing of the necrotic area is complete.

3. There are strong suggestions that much of so-called chronic brucellosis is more accurately conceived as an intrinsic brucellar hypersensitiveness rather than as an active propagation or progressive invasion of living Brucella organisms.

4. Hyposensitization brings about improvement in chronic brucellosis and in the symptoms of hypersensitiveness associated with this condition.

5. There are, however, some patients with such severe degrees of hypersensitization to Brucella vaccine that no dose has yet been found small enough which they can tolerate well. This fact requires further study, both theoretically and practically.

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REFERENCES

1. Angle, F. E.; Algie, W. H.; Baumgartner, L., and Lindsford, W. F.: Skin testing for brucellosis in school children. Ann. Int. Med., 12:495, (Oct.) 1938.
2. Angle, F. E., and Algie, W. H.: Chronic brucellosis: an analytical study of the positive reactors among school children. Ann. Int. Med., 12:1189, (Feb.) 1939.
3. Buddingh, G. J., and Womack, F. C., Jr.: Observations on the infection of chick embryos with Bacterium tularense, Brucella and Pasteurella pestis. J. Exper. Med., 74:213-222, (Sept. 1) 1941.
4. Darley, W., and Gordon, R. W.: Brucella sensitization: a clinical evaluation. Ann. Int. Med., 26:534, (April) 1947.
5. de Villefañe, T.: Espondilitis melitococcica. Anales de la Clinica Medica "C," 3:23-65, 1942. Córdoba, Argentina.
6. Fondé, G. H.: Hypersensitization, a phase in chronic infectious diseases, a clinical study. J.M.A., Alabama, 16:6, (July) 1946.
7. Foshay, L.: The laboratory diagnosis of undulant fever. Am. J. Clin. Path., 10:176-187, (Feb.) 1940.
8. Foshay, L.; Hesselbrock, W. H.; Wittenberg, H. V., and Rodenberg, A. N.: Prophylactic vaccination against tularemia in man. Am. J. Pub. Health, 32:1131-1145, (Oct.) 1942.

9. Gersh, I, and Mugrage, E. R.: The incidence of positive immunologic reactions for undulant fever. J. Lab. & Clin. Med., 23:918, (June) 1938.
10. Goodpasture, E. W.: The cell-parasite relationship in bacterial and virus infection. Tr. Coll. Physicians, Philadelphia, 9:11-24, (April) 1941.
11. Gould, S. E., and Huddleson, I. F.: Diagnostic methods in undulant fever (brucellosis) with results of a survey of 8,124 persons. J.A.M.A., 109:1971, (Dec. 11) 1937.
12. Griffith, G. C.: Rheumatic fever. J.A.M.A., 133:974, (April 5) 1947.
13. Griggs, J. F.: Chronic brucellosis: diagnostic points noted in 100 cases. California & West. Med., 58:118-124, (March) 1943.
14. Griggs, J. F.: Specific vaccine therapy of chronic brucellosis. J. Indiana M. A., 37:241-245, (May) 1944.
Griggs, J. F.: Chronic brucellosis: conclusions on treatment after ten years. J.A.M.A., 136:911-915, (Apr. 3) 1948.
15. Harris, H. J.: Brucellosis (Undulant Fever), Clinical and Sub-clinical. New York: Paul B. Hoeber, Inc., 1941.
16. Harris, H. J.: Brucellosis: advances in diagnosis and treatment. J.A.M.A., 131:1485-1493, (Aug. 31) 1947.
17. Huddleson, I. F.; Hardy, A. V.; Debono, J. E., and Giltner, W.: Brucellosis in Man and Animals. New York: The Commonwealth Fund, 1943.
18. Kirby, W. M. M., and Rantz, L. A.: The agglutinin response of normal persons to skin tests with brucellergen and brucella vaccine. J. Lab. & Clin. Med., 27:1244-1248, (July) 1942.
19. Kulowski, J.: Undulant fever osteomyelitis and arthritis. Surg., Gynec., & Obst., 62:759-764, 1936.
20. Menefee, E. E., Jr., and Poston, M. A.: Significance of standard laboratory procedures in diagnosis of brucellosis. Am. J. M. Sc., 197:646-653, 1939.
21. Meyer, K. F.: Observations on the pathogenesis of undulant fever. Essays in Biology. Univ. of California Press, 1943.
22. Rabson, S. M.: Pathologic anatomy of human brucellosis. Am. J. Clin. Path., 9:604, 1939.
23. Rössle, R.: Beitrag zur Kenntniss der geweblichen Veränderungen bei der Bangschen Krankheit des Menschen. München. med. Wchnschr., 80:5-6, (Jan. 6) 1933.
24. Rössle, R.: Die geweblichen Äusserungen der Allergie. Wien. klin. Wchnschr., 45:609-613, (May 13), 1932; 45:648-651, (May 20) 1932.
25. Sandstrom, O.: Multiple spondylitis in undulant fever. Acta Radiol., 18:253, 1937.
26. Small, W. S.; Hawes, R. C.; Miller, H., and Piness, G.: Contamination of antigens with traces of other antigens as a cause of false positive reactions in intradermal testing. J. Allergy, 13:380-384, (May) 1942.

SKIN REACTIONS XVI

(Continued from Page 328)

REFERENCES

1. Aaron, T. H., and Abramson, H. A.: Inhibition of histamine whealing in human skin by Pyribenzamine hydrochloride using iontophoretic technic. Proc. Soc. Exper. Biol. & Med., 65:272, 1947.
2. Abramson, H. A., and Alley, A.: Skin reactions I. Mechanism of histamine iontophoresis from aqueous media. Arch. Phys. Therap., 18:327, 1937.
3. Abramson, H. A., and Engel, M.: Skin reactions II. The effect of allergic and histamine wheals on the rate of absorption of dyes and blood from the human cutis. J. Invest. Dermat., 1:65, 1938.
4. Abramson, H. A., and Gettner, H. H.: Skin reactions XI. Lymphatic escape following electrophoresis of histamine and epinephrine. J. Invest. Dermat., 4:243, 1941.
5. Abramson, H. A., and Ochs, I.: Skin reactions VI. A simple micromethod for the assay of histamine in mammalian blood. J. Lab. & Clin. Med., 24: 398, 1938.
6. Bender, M. B.; Abramson, H. A., and Ehrlich, G.: Skin reactions XIV. The effect of atropine on the mecholyl and whealing reactions of the skin. J. Mt. Sinai Hosp., 9:No. 4, 1942.

THE DIAGNOSIS AND TREATMENT OF PERENNIAL ALLERGIC CORYZA

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PERENNIAL allergic coryza is one of the most common upper respiratory tract conditions and, perhaps, the most neglected. Its successful treatment is entirely dependent upon integrating several therapeutic measures, not any one of which is sufficient to produce prolonged and sustained improvement. For the purpose of this paper, perennial allergic coryza is synonymous with vasomotor rhinitis, allergic rhinitis, nasal asthma, atopic coryza, nonseasonal hay fever, hypersthetic rhinitis, et cetera. The term perennial allergic coryza completely describes the continued nonseasonal time element, the etiologic nature, and the anatomical structures of the symptom complex involved.

CLINICAL DIAGNOSIS

Statistics.—Data recorded from a study of 180 cases of perennial allergic coryza, obtained from private practice over a period of two years, are presented. In our series, the syndrome affected females more often than males—100 (55.6 per cent) against eighty (44.4 per cent). At the time at which the patients presented themselves for treatment, 124 (68.8 per cent) were under forty years of age while fifty-six patients (31.2 per cent) were over forty years. Many had had their symptoms for as long as ten to twenty years. Undoubtedly, if the age of onset was considered, many of the older age group would be classified in the younger age brackets. According to our records, the age incidence was: in the first decade, twenty cases; in the second, thirty-six; in the third, twenty-eight; in the fourth, forty; in the fifth, twenty-eight; in the sixth, twenty-one; in the seventh, seven. A positive family history of allergy was obtained in 114 cases (63.3 per cent), while sixty-six patients (36.7 per cent) gave a negative history of any allergic manifestation appearing in the family. In the former group, thirty-eight patients (21 per cent) gave a bilateral family history of allergy, while seventy-six patients (42 per cent) presented a positive unilateral history. Careful and patient interrogation was required to elicit this information, because oftentimes either the patient or the parent is unaware of an allergic syndrome existing in the family tree or, perhaps, the parent is reluctant to make the admission, thinking that it is personally incriminating.

Syndrome Combinations.—Other allergic manifestations are often associated with perennial allergic coryza. It very frequently occurs with bronchial asthma and pollinosis, and less often with colitis, migraine,

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TABLE I. INCIDENCE OF ALLERGIC SYNDROME COMBINATIONS

(The Predominant Syndrome is Listed First)

Perennial allergic coryza	61 cases (33.8%)
Perennial allergic coryza and bronchial asthma	36 cases (20%)
Bronchial asthma and perennial allergic coryza	20 cases (11.1%)
Perennial allergic coryza, pollinosis, and bronchial asthma	27 cases (15%)
Bronchial asthma, pollinosis, and perennial allergic coryza	14 cases (7.7%)
Perennial allergic coryza and pollinosis	10 cases (5.5%)
Perennial allergic coryza and colitis	4 cases (2.2%)
Perennial allergic coryza and migraine	2 cases (1.1%)
Perennial allergic coryza, bronchial asthma, and migraine	1 case (0.5%)
Perennial allergic coryza, pollinosis, bronchial asthma, and migraine	1 case (0.5%)
Perennial allergic coryza, pollinosis, and eczema	1 case (0.5%)
Perennial allergic coryza, bronchial asthma, and eczema	1 case (0.5%)
Perennial allergic coryza and urticaria	1 case (0.5%)
Perennial allergic coryza, pollinosis, bronchial asthma, and angioneurotic edema	1 case (0.5%)

TABLE II. PERCENTAGE RATIO OF CAUSATIVE FACTORS IN PERENNIAL ALLERGIC CORYZA

Extrinsic	Intrinsic	Combined Extrinsic—Intrinsic	Total
1 case 0.6%	36 cases 20%	143 cases 79.4%	180 cases 100%

eczema, urticaria, and angioneurotic edema. The incidence of allergic syndrome combinations as noted in our study is presented in Table I.

The most important and distressing complication of perennial allergic coryza is bronchial asthma. This occurred in thirty-six cases (20 per cent). In another twenty cases (11.1 per cent), it was associated as a subdominant allergic manifestation with primary bronchial asthma. In still another group of forty-five cases (25 per cent), it was combined with bronchial asthma in association with other allergic syndromes.

ETIOLOGIC DIAGNOSIS

From an etiologic standpoint, the causes of perennial allergic coryza can be divided into two classes: the nonspecific and specific. The nonspecific causes are particularly sudden changes in temperature, smoke, pungent odors, paint and gas fumes. Though these factors may aggravate or precipitate an exacerbation, they are rendered impotent when the specific causes are controlled. The specific causative factors are inhalants, ingestants, and bacterial haptens. These can be divided into three groups: (1) the extrinsic, (2) the intrinsic, and (3) the combined.

Extrinsic Group.—In the extrinsic group, the specific causative factors are of exogenous origin and consist of inhalants (other than pollen) and ingestants. In analyzing our cases, it was found that the extrinsic group was very small. It has been our experience that practically all the patients with perennial allergic coryza of more than several months' duration, due solely to extrinsic causative factors, very quickly develop a sensitivity to bacterial products. Thus, this group is constantly fluctuating. With the advent of a bacterial sensitivity, these patients merge into the combined extrinsic-intrinsic group. In the entire series, only one case (0.6 per cent) did not develop a secondary bacterial sensitivity (Table II).

Intrinsic Group.—The most important causative factors in the intrinsic group are the endogenous products of bacterial activity. In the complete series, thirty-six patients (20 per cent) (Table II) had a bacterial sensitivity only, hence belong to this group. These patients presented a history of frequent head colds, each of which lasted much longer than the rather short duration (four to ten days) of an acute coryza. The symptoms merged gradually from an acute to a prolonged subacute stage. The latter lasts indefinitely until a fresh insult precipitates the cycle. With each fresh exacerbation, the thin watery discharge becomes a mucopurulent one in which a neutrophilic picture prevails. Slowly, as the character of the discharge again becomes thin and watery, the eosinophiles replace the neutrophiles. The nasal mucous membrane has a dusky red color, and the lower turbinates are boggy and edematous. Sneezing, chronic rhinorrhea, slight itching of the nose, nasal voice, frontal headache, and lassitude were constantly noted. This is the clinical picture of bacterial nasal allergy and is analogous to bronchial asthma of bacterial origin. One might hypothesize a combination of bacterial hapten based upon the Burky phenomenon[4] as a possible explanation for bacterial nasal allergy.

From an etiologic point of view, bacterial allergy of the nose has not received the proper recognition from both allergists and rhinologists. In the past, the bacterial phase of perennial allergic coryza has been categorically classified as chronic infection. In the differential diagnosis insufficient attention has been given to the history, character of the nasal discharge, and the correct interpretation of repeated nasal smears. Perhaps, the classical description of the pale grayish blue color of the nasal mucous membrane has been overemphasized. An allergic nose can and does occasionally present a dusky red mucous membrane. This is not an irreversible reaction, because with proper conservative and specific treatment the normal color can be restored. A comparable duskiness has been noted in the intestinal tract at laparotomy. Marks[3] states that a preoperative diagnosis of acute appendicitis sometimes may become, upon entering the abdomen, a postoperative diagnosis of gastrointestinal allergy characterized by segmental spasm and duskiness occasionally associated with a small amount of bloody exudate. The administration of epinephrine hydrochloride parenterally immediately relieves the spasm and restores the normal color to the affected intestine.

Combined Extrinsic-Intrinsic Group.—This is a very large group, 143 cases (79.4 per cent) being classified in it (Table II). All of these cases at first presented a single or multiple sensitivity, originally due to extrinsic factors. However, with the advent of repeated bouts of nasal infection, a bacterial hapten sensitivity (intrinsic) insidiously developed. Thus, these patients slowly merged into the combined group. This group also includes the patients with pollinosis who complicated their pollen sensitivity with

bacterial nasal allergy. Patients in the combined extrinsic-intrinsic group are really never free of their complaint because the interaction of the causative factors continuously exacerbates their symptoms.

TABLE III. CAUSATIVE FACTORS OF PERENNIAL ALLERGIC CORYZA IN A STUDY OF 180 CASES

1. Kapok (single sensitivity)	1 case	(0.6%)
2. Bacterial hapten sensitivity	36 cases	(20.0%)
3. Single or multiple inhalant and/or ingestant sensitivities in combination with bacterial hapten sensitivity	143 cases	(79.4%)
(a) House dust	94 cases	
(b) Pollens	54 cases	
(c) Foods	37 cases	
(d) Kapok	12 cases	
(e) Dog dander	6 cases	
(f) Cat dander	6 cases	
(g) Feathers	5 cases	
(h) Molds	1 case	
(i) Drugs (aspirin)	1 case	

Skin Tests.—A most essential procedure in establishing the etiologic diagnosis is the correct evaluation of skin tests.[2] The most common causes (Table III), excluding bacterial haptens, were, in the order named, house dust, pollens, foods, kapok, dog and cat dander, feathers, and molds. The major food offenders were cheese, egg, chocolate, shellfish, milk, cereals, spinach, apple, nuts, and banana. The less common food offenders were grapefruit, cucumber, pork, asparagus, tomato, coffee, beets, and mushroom.

Diagnostic Criteria.—The establishment of a clinical and accurate etiologic diagnosis of perennial allergic coryza entails the following pertinent essentials: (1) a thorough history with special emphasis upon the allergic phase, (2) a complete physical examination including routine blood and urine studies, (3) skin tests interpreted and correlated with the allergic history, (4) repeated observations of nasal smears, and (5) x-ray of the paranasal sinuses. Often, despite all these studies and not until the patient demonstrates a continuous clinical improvement, can a physician be absolutely certain that the correct etiologic diagnosis has been established.

TREATMENT

The conservative approach is the keynote to successful treatment. It is based upon the integration of several therapeutic procedures, each one of which when employed singly, indiscriminately, or out of sequence either fails or, at best, produces minimal improvement only. In the treatment of perennial allergic coryza, allergic therapy is the primary medical approach, while rhinologic surgery is secondary and should be reserved for the treatment of allergic complications such as polyps, boggy turbinates, and inadequate drainage. Rhinologic surgery should be employed only after the allergic regimen has been in operation for several months because sometimes, with proper allergic therapy, nasal polyps do disappear, edematous turbinates do return to normal, and adequate drainage can be re-established.

Allergic Hygiene.—Factors which constantly aggravate the patient's complaint must be excluded from the immediate environment. The patient

is instructed to avoid contact with irritating odors from leaky gas or oil stoves, kerosene lamps, gasoline and oil products, electric refrigerators, fresh paint, tobacco smoke, tar, camphor, et cetera. Insect powder is not to be used in the home. The usual dust precautions must be followed. Unless specifically advised, animal pets are not to be kept. Smoking, if not completely eliminated, is to be reduced to a minimum. Protection against exposure to inclement weather and sudden changes in temperature is essential, since the patient must prevent as many bouts of upper respiratory infection as possible. An adequate amount of restful sleep, at least eight hours nightly, is highly desirable. Drugs should be taken only upon prescription. Finally, all foods to which the patient is sensitive are to be eliminated from the diet.

Outline of Treatment—The following therapeutic measures have been integrated in their proper sequence and, in our hands, have produced highly gratifying results. It cannot be emphasized too strongly that these measures are supplementary to each other and will fail if employed singly. To obtain optimum results, the therapeutic chain must be used in its entirety.

A. Office Procedures.
   1. Nasal decongestants.
   2. Penicillin aerosol intranasally.
   3. Mild silver protein nasal spray.
   4. Desensitization.
   5. Vaccine therapy.

B. Supportive Measures.
   1. Decongestants and mild silver protein nasal sprays.
   2. Antihistamine drugs.
   3. Multiple vitamins oral therapy.

C. Intranasal Surgery.

Office Procedures

Decongestants.—The first step in our treatment is the intranasal administration of a small amount of aqueous ephedrine 1 per cent isotonic solution in heated vapor form. This is followed by a warm spray of Gluco-thricil (an isotonic solution of ephedrine 1 per cent and Tyrothricin 1:5000).

Penicillin Aerosol Intranasally.—A very important agent in the armamentarium of the allergist for the treatment of perennial allergic coryza is nebulized penicillin aerosol intranasally. Crystalline sodium penicillin G, in concentration of 50,000 units per c.c. of distilled water, is combined with 1 c.c. of a 1 per cent isotonic solution of Neo-synephrine hydrochloride. One half c.c. of this solution, containing approximately 12,500 units of penicillin and 3½ minims of 1 per cent Neo-synephrine, is aerosolized at each treatment. In more than 1,000 such treatments, not a single penicillin reaction has been encountered. If the symptoms are severe,

intranasal penicillin aerosol therapy can be administered every other day for three or four treatments; otherwise, once weekly will suffice. An average of six to eight penicillin aerosol treatments will produce highly beneficial results. Oftentimes, only one or two treatments are responsible for a dramatic amelioration.

Mild Silver Protein Nasal Spray.—The intranasal penicillin treatment is followed by a mild silver protein (argyrol type) nasal spray, 10 per cent strength.

Desensitization.—Specific desensitization is not neglected. House dust, pollens, animal dander, and molds receive special attention as indicated. Offending foods can be eliminated from the diet. If this is not practical, oral desensitization can be tried.

Vaccine Therapy.—In our series, bacterial hapten sensitivity was the sole causative factor in thirty-six cases (20 per cent) and a secondary complicating factor in 143 cases (79.4 per cent). Thus, bacterial hapten sensitivity has a phenomenally high incidence. All of these patients were treated with a stock vaccine suspension containing the following organisms, each in concentrations of 200 millions per c.c.: Micrococcus catarrhalis, Bacillus friedlander, Pneumococcus (Types I, II, III), Streptococcus (hemolyticus and viridans), Staphylococcus albus, and Staphylococcus aureus. Injections were given with a syringe graduated in tenths, smaller doses intradermally, larger ones subcutaneously. The first six doses were given at weekly intervals, while subsequent doses, depending upon the clinical progress, were administered either weekly or monthly. The initial dose should be 0.05 c.c., the second 0.1 c.c., the third 0.2 c.c., the fourth 0.3 c.c., the fifth 0.4 c.c., and the sixth 0.5 c.c. At this point, if the symptoms were well controlled, the seventh dose (0.75 c.c.) and the eighth dose (1.0 c.c.) were administered. The latter was repeated at monthly intervals indefinitely. If, however, the patient still had some complaint, the dosage was levelled off at 0.5 c.c. This dose was repeated at weekly intervals until the residual nasal symptoms disappeared, at which time the 0.75 c.c. and 1.0 c.c. doses were given. With this schedule only exceedingly mild constitutional reactions have been encountered, the symptoms consisting of slight headache and malaise which disappeared in a few hours. Vaccine therapy very often produces a spectacular improvement.

Supportive Measures

The patient is instructed to use locally Gluco-thricil solution, a *decongestant, antibiotic nasal spray* followed by a *mild silver protein spray* of the argyrol type (10 per cent strength) twice daily. Decongestants must be employed for a short time only. Kern[1] emphasizes that the too frequent and excessive use of vasoconstrictor drugs is followed by a vasoparalysis and a consequent increase of mucosal edema. Apparently valuable additions to our therapeutic measures have been the introduction of *antihista-*

mine drugs. Employed in recommended doses, they seem to exert a beneficial influence upon the symptoms of perennial allergic coryza and are effective in about 50 per cent of the cases. Potent *multiple vitamins* were administered routinely to all the patients. Within a comparatively short time, they experienced a feeling of well-being, became more alert, and regained their appetite. The administration of these vitamins, because of their tonic effect, was continued indefinitely.

Intranasal Surgery

Edematous turbinates, mucous polyps, and inadequate drainage are often observed in long-standing cases of perennial allergic coryza. If these local complications do not completely disappear or, at least, greatly improve after several months of allergic therapy, then surgical intervention should be considered. When, however, early operation is essential because of the gravity of the complications, subsequent allergic therapy should not be neglected; otherwise, the symptoms persist and the complications, especially nasal polyps, tend to recur. A competent rhinologist should perform the indicated surgical procedures.

RESULTS

The treatment, as described, has produced uniformly excellent results. The nasal symptoms were markedly improved after six to eight weekly treatments. In many patients, a spectacular amelioration was noted after only one to two treatments. Sneezing, itching, nasal discharge, postnasal drip, nasal voice, and frontal headache quickly disappeared. Besides local amelioration the patients also experienced an improvement in their general health. They felt stronger, were more alert and eager, and their appetites improved. In our series of 180 cases, 149 patients (83 per cent) received 100 per cent improvement; twenty-four patients (13 per cent) had 75 per cent; five patients (3 per cent) had 50 per cent. There were two failures (1 per cent), patients in whom no improvement was noted or their symptoms were made worse.

CONCLUSIONS

Perennial allergic coryza is a disease entity. Bacterial haptens, inhalants, and ingestants are the commonest specific causative factors. Its successful treatment depends upon the application of several therapeutic measures, each properly integrated to form a therapeutic chain which embodies the allergic approach as the primary essence of treatment and reserves rhinologic surgery for the treatment of the allergic complications only. Conservative and judicious therapy will produce excellent clinical results.

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REFERENCES

1. Kern, R. A.: Perennial allergic rhinitis: the most important respiratory allergy. M. Clin. North America, 1375-1392, (Nov.) 1947.
2. Maietta, A. L.: A critical evaluation of skin tests in allergy. Maine M. J., 31: 105, 1940.
3. Marks, G. A.: Personal communication.
4. Vaughan, W. T.: Practice of Allergy. St. Louis: C. V. Mosby Co., 1939.

A NEW ANTIHISTAMINIC COMPOUND FOR THE TREATMENT OF URTICARIA AND HAY FEVER

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AT least 200 drugs have been offered on the market for the treatment of urticaria and hay fever; but in spite of this large assortment from which to choose, the results have often been inadequate and unsatisfactory. In urticaria, the subcutaneous injection of epinephrine or oral administration of ephedrine might give partial and transient relief from the pruritus. Calcium has been advocated because of its ability to decrease the excitability of the nervous system, but it has produced no detectable relief except when injected intravenously in large doses. When epinephrine, ephedrine, and intravenous calcium have failed, the physician has turned to less hopeful products, as, for example, alkalis, atropine, and the sedatives. The local application of calamine lotion and similar solutions has been of little help. In hay fever, orally administered ephedrine and the topical application of vasoconstrictors have been perhaps the most widely used symptomatic treatments, but they have left much to be desired.

Allergists have, therefore, searched for new drugs which might be useful and have welcomed the appearance of the antihistaminic compounds with some enthusiasm.

The earliest antihistaminic drugs to become available in this country were Benadryl and Pyribenzamine. The excessive drowsiness resulting from Benadryl was a disadvantage. A twenty-eight-year-old woman patient under my care slept for seventy-two hours after taking 50 mg. The incident caused me so much concern that I hesitated to use Benadryl thereafter. Pyribenzamine did not cause the same degree of drowsiness. It was helpful in many cases but failed in many others.

On August 12, 1947, I obtained a supply of Histadyl (Thenylpyramine Hydrochloride, Lilly).* It was thus possible to investigate the usefulness of this drug during the ragweed hay fever season which ordinarily begins in Chicago about August 15. The pharmacology of Histadyl had been reported by Lee, Dinwiddie, and Chen,[1] and a preliminary clinical report was given by Peirce and Mothersill.[2] Chemically the compound is a derivative of ethylenediamine. Its graphic formula is shown on the following page.

DOSAGE AND RESULTS

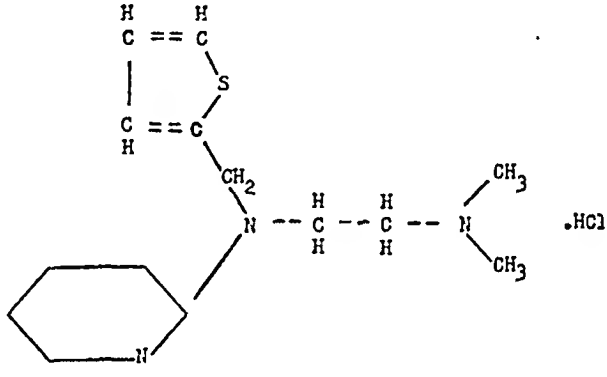
The dosage ordinarily used for hay fever in children was a 25-mg. capsule three to five times daily. For adults, each dose was 50 mg. given in the same manner. In urticaria it was usually necessary to give doses twice as large as in hay fever. A total of twenty-seven patients were treated. The results are given in Table I.

*This compound was originally designated by its laboratory serial number, 01013.

TABLE I.

Type of Allergy	No. of Cases	Results
Hay fever	21	Moderately good to excellent
Urticaria	4	Good to excellent
Serum sickness	1	Excellent
Asthma	1	No value

In hay fever cases, excellent results were obtained only in patients who had received a preseasonal and coseasonal course of injections with allergenic ragweed pollen extracts. Patients who had not had this treatment obtained less satisfactory relief. In order to obtain good to excellent results in urticaria, it was necessary to prescribe 400 to 500 mg. of the drug daily. The drug failed to help the first asthmatic patient treated, and since other antihistaminics had also failed in asthma I preferred to use my limited supply of Histadyl in cases where there was more hope of benefit.



Graphic formula of Histodyl

TOXIC EFFECTS

Three hay-fever patients complained of a dull frontal headache for ten to thirty minutes after taking Histadyl. However, this was not sufficiently serious to justify discontinuation of the drug. Definite drowsiness was not observed, but in most cases there appeared to be a feeling of relaxation. This was desirable in those who were otherwise apprehensive.

Blood counts, urine analyses, and blood pressure readings were obtained in patients who took the drug for six to ten weeks. Systolic blood pressures had a tendency to become lower by 10 to 15 mm. No significant blood or urine variations were noted.

SUMMARY

1. A report of twenty-seven allergic patients treated with Histadyl is given.

2. Except for one asthmatic patient, the results were moderately good to excellent.

3. In ragweed hay fever, excellent results were obtained only in those

(Continued on Page 383)

AN EVALUATION OF THE PATCH TEST BASED ON EXPERIMENTAL FINDINGS

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THE purpose of the patch test is the reproduction of the clinical skin lesion on an uninvolved local area. Since no prior preparation of the skin is entailed, the patch test is also referred to as the surface, contact, or percutaneous test. A positive reaction represents a delayed type of allergic response, the reaction time being approximately twenty-four hours.

The preponderance of evidence fails to substantiate the presence of detectable antibody or the transfer of sensitivity through serum or vesicle fluid. Though the studies of Landsteiner and his co-workers[10] in chemical hypersensitiveness in animals have demonstrated wheal-type antibodies and passive transfer of sensitiveness, these phenomena have not been substantiated in contact dermatitis in humans.

TABLE I. SPONTANEOUS FLARE-UP OF SITES IN SUBJECTS SENSITIZED BY ONE APPLICATION OF EXCITANT—THE INCUBATION PERIOD

Excitant	Number of Subjects	Period of Application	Incubation Period—Interval between Application and Flare-up
Krameria fluid-extract 1.0 g. in 1.0 ml.		Days	Days
	5 adults	1	10–21
	2 adults	2	11–12
	1 adult	3	11
	6 adults	7	9–14
	4 children	2	8–15
Limits	18 subjects	1–7	8–21

When a chemical substance, simple or complex in nature, which has shown its ability to act as a potent sensitizing agent is applied experimentally to the human skin, phenomena of both theoretical and clinical importance are observed. One such excitant is krameria,[5] a plant extractive, which has been used by the writer in a series of studies in contact allergy in humans. Thus, application to the skin by patch test of several drops of the fluid extract of krameria for a period of one, two, three, or seven days was followed by the appearance of a contactant-type reaction (papular or vesicular dermatitis) after a lapse of from ten to twenty-one days following the onset of the exposure (Table I). This response was referred to as the flare-up phenomenon.[5,6] The interval between treatment of a site and the appearance there of a reaction was the incubationary period of sensitization of human skin with krameria, and signified the advent of a state of hypersensitiveness in an individual previously non-sensitive. Subsequent testing in the same manner elicited a typical response on removal of the patch test at the end of twenty-four hours or less. This shortened period represented the reaction time in an already sensitive subject. Moreover, it was evident that the entire skin surface was involved, for applica-

TABLE II. SPONTANEOUS FLARE-UP OF SITES IN SUBJECTS SENSITIZED BY THREE APPLICATIONS OF EXCITANT

Case Number	Duration in Days of Applications 1 and 2	Day of Application 2	Reaction After Application	Day of Application 3	Day of Reaction at Site 3	Day of Flare-up at Site 2	Day of Flare-up at Site 1	Inactive Phase of Site 2	Inactive Phase of Site 1
9	2,1 resp.	15	0	22	(24)–29*	(25)–29		(10)–14	
10	1,1 resp.	92	0	99	(109)–106	(102)–106		(10)–14	
11	1,1 resp.	29	0	36	(?)–43**	(?)–42		(?)–14	
12	7,1 resp.	29	0	36	(?)–50	(?)–50		(?)–21	
13	2,1 resp.	15	0	22	(?)–29	(?)–36	(?)–43	(?)–21	(?)–43
14	7,1 resp.	15	0	22	(23)–29	(26)–29	(29)–29	(11)–14	(29)–29

*Number indicates day on which writer observed reaction.
Number in ( ) indicates day on which subject observed reaction.
**(?) signifies that subject did not observe the exact day on which reaction appeared. The reaction obviously occurred from one to seven days prior to its observation by the author.

tion of the test to any part of the body was followed by the appearance of the typical reaction.

Subjects who failed to become sensitized by the initial treatment could become so upon repetition of the patch tests to other areas at intervals of one or several weeks. Thus, nineteen subjects were sensitized by two to five successive applications of the excitant. Moreover, the appearance of a response at the final site of treatment was followed in fifteen subjects by a spontaneous flare-up of the site of the preceding application which up to that time had remained unchanged (Table II). In four additional subjects flare-up occurred at two preceding and previously negative test sites. The interval which elapsed between the time of the treatment of these late responding areas and the appearance of the spontaneous reactions at these sites was from ten to forty-three days, referred to in the tables as the inactive phase. It would appear from these findings that allergenic excitant applied to the surface of the skin had become fixed in the skin cells for as long as forty-three days.

It was observed, furthermore, that flare-up of the sites occurred in the reverse order of treatment, i.e., the final site first, the preceding one next, et cetera, and that the delayed responses were in most instances of lesser intensity than the initial flare-up reactions. To obtain an explanation for this phenomenon, the flare-up reaction was studied further, using graded dilutions of the excitant. The findings indicated that the earliest treated sites had lost most of the excitant, and that their reactivity had diminished during the inactive phase so that it was equivalent to that elicited by a solution many thousand times weaker than the original extract. Thus the spontaneous flare-up of sites in the reverse order of their treatment indicated waning amounts of fixed allergenic substance at the respective areas.

Another study, recently reported,[7] demonstrated that a healed site of contact dermatitis responded to nonspecific stimulation by direct treatment with a second contactant, whereas adjacent uninvolved skin remained non-

reactive. While these findings were primarily related to the subject of so-called local skin sensitivity and the performance of patch tests on healed dermatitis areas, they would suggest, in addition, that antigenic substance remained fixed in the skin at healed specific sites for as long as 128 days.

In summary, then, the cited studies indicate the possibility of sensitizing the entire skin surface by means of the patch-test application of a potent chemical substance in sufficiently high concentration. The allergenic excitant is apparently fixed in the skin and evokes an immunologic response which may or may not be adequate to produce total sensitization. Successive patch test treatments then may evoke such an effect, each single stimulus playing its own cumulative part to bring about the final state of hypersensitiveness.

The clinical implications would seem obvious, namely that diagnostic patch tests with an active excitant in high concentration may induce sensitization even with a twenty-four or forty-eight hour contact. There are a number of reports in the literature giving the incidence of sensitivity to poison ivy as 49 to 76 per cent, whereas analysis of the findings indicate that in many of the subjects sensitivity had been induced by the patch test itself.[3,8,9,11,15,16] A knowledge of the sensitizing potencies of chemicals, as pointed out by Sulzberger[17] and others would minimize such a hazard. Secondly, the not uncommon practice of repeating patch tests with the same allergen, when reactions are negative or doubtful, should be discouraged, since each such exposure can act as an immunological stimulus. It is not improbable, therefore, that the repetition of certain diagnostic patch tests by one or several clinicians may actively sensitize patients to contactants being applied in the tests. The risk from indiscriminate patch testing becomes even more apparent when it is carried out by untrained personnel, including lay cosmeticians.

As another clinical implication, the findings that nonsensitive areas of skin and healed sensitive sites are able to fix allergenic excitant help to explain a number of clinical experiences reported in the literature and undoubtedly encountered occasionally by practicing dermatologists and allergists, namely:

1. The relighting of healed patch-test sites by a repetition of the test with the same substance.[12]
2. The exacerbation of a quiescent or recently healed dermatitis, following patch testing with the specific substance.[4] Actual spreading of the dermatitis may likewise ensue.[1]
3. The relighting of healed patch-test sites following a recurrence of the specific dermatitis.[2]

SUMMARY

Experimental studies in sensitization of the skin of humans indicated that the patch test may be a means of provoking sensitization of the nonsensitive individual. It was also evident that excitant can remain fixed in

the skin for relatively long periods of time. To avoid the hazards incident to the clinical implications of these findings, certain precautions must be observed in the performance of patch tests.

1. The nonsensitizing concentrations of contactants should be known. Detailed lists of excitants may be consulted.[11,13,17,18]

2. Tests with the same or related excitants should not be repeated under certain conditions.

3. Patch tests should not be applied during the active phase of a dermatitis or a recently subsided dermatitis.

4. A patch test with the specific excitant may produce the generalization of a localized active dermatitis.

5. Local testing in previously involved areas may give nonspecific reactions which are not of etiologic significance.

REFERENCES

1. Bechet, P.: The patch test. An evaluation of its possible dangers. New York State J. Med., 39:829, 1939.
2. Counter, C. E.: Recurrent reaction to patch test. Arch. Dermat. & Syph., 37:495, 1938.
3. Deibert, O., Menger, E. F., and Wiggelsworth, A. M.: Studies in specific hypersensitiveness. Relative susceptibility of the American Indian race and the white race to poison ivy. J. Immunol., 8:287, 1923
4. Epstein, E.: Untoward reactions to patch tests. J. Invest. Dermat., 5:55, 1942.
5. Grolnick, M.: Studies in contact dermatitis. III. Active sensitization with krameria in man. J. Invest. Dermat., 1:179, 1938.
6. Grolnick, M.: Studies in contact dermatitis. IV. The spontaneous flare-up of negative test sites in experimental sensitization in man. J. Immunol., 41:127, 1941.
7. Grolnick, M.: Studies in contact dermatitis. VII. The response of healed specific dermatitis sites to stimulation with another contactant. Read at the annual meeting of the American Academy of Allergy, Dec. 17, 1947.
8. Keeney, E. L., Sunday, S., Gay, L. N., and Lynch, K.: Poison ivy dermatitis; diagnostic value of patch test made with ether extract from fresh leaves and stems of poison ivy plant. Bull. Johns Hopkins Hosp., 69:482, 1941.
9. Knowles, F. C., Decker, H. B., Pratt, A. G., and Clarke, Jr., A. J.: Susceptibility of allergic and nonallergic persons to rhus toxicodendron Arch Dermat. & Syph., 38:773, 1938.
10. Landsteiner, K.: The Specificity of Serological Reactions. Cambridge, Mass.: Harvard University Press, 1946.
11. Mayer, R. L.: Das Gewerbeekzem. Berlin: Julius Springer, 1931.
12. Mueller, A.: Active sensitization with ursol. Dermat. Zeitschr., 61:241, 1931.
13. Schwartz, L.: Sensitivity to external irritants in industry. New York State J. Med., 36:1969, 1936.
14. Spain, W. C.: Studies in specific hypersentitiveness. VI. Dermatitis venenata. J. Immunol., 7:179, 1922.
15. Spain, W. C., Newell, J. M., and Meeker, M. G.: The percentage of persons susceptible to poison ivy and poison oak. J. Allergy, 5:571, 1934.
16. Straus, H. W.: Artificial sensitization of infants to poison ivy. J. Allergy, 2:137. 1931.
17. Sulzberger, M. B.: Dermatologic Allergy. Springfield, Ill.: Charles C Thomas, 1940.
18. Urbach, E.: Klinik und Therapie der Allergischen Kronkheiten. Vienna: Wilhelm Maudrich, 1935.

AN ADAPTER FOR THE RAPID PERFORMANCE OF THE PUNCTURE SKIN TEST

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A SIMPLE adapter for the allergy syringe which facilitates the rapid and uniform performance of the puncture skin test has been devised. The adapter is processed from stainless steel or other suitable metal, and consists of a lateral component about two inches long and two horizontal extensions. The proximal extension consists of a split circular band, which by virtue of its spring action fits snugly around the barrel. The distal component is bored to allow movement of the needle up to its hub. The lateral component rests parallel to the barrel of the syringe, and serves to adjust the adapter upward or downward.

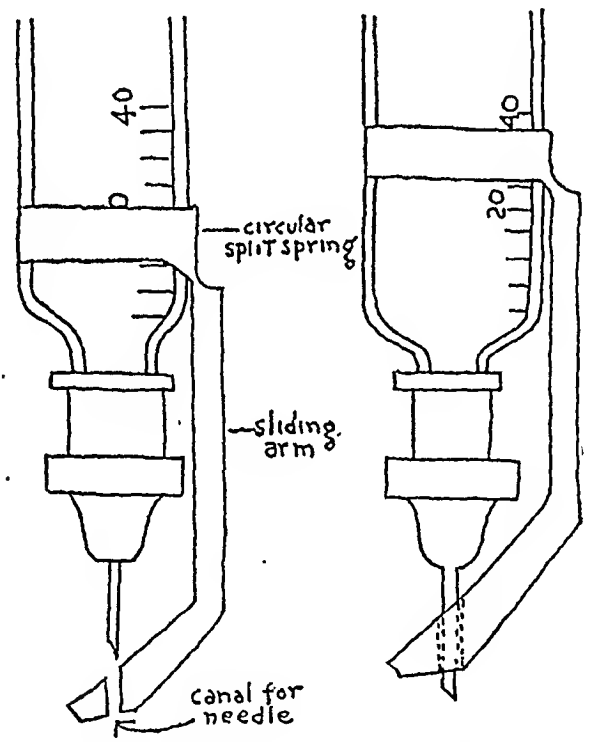

Fig. 1. Adapter for puncture skin testing.

OPERATION

The adapter is slipped over the barrel of the syringe, the hypodermic needle is then attached and the allergen drawn up.

The desired depth of the needle exposed for puncture is obtained by the appropriate adjustment of the adapter.

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TECHNIQUE

The depth of the needle exposed in each case should be determined by the performance of a few preliminary puncture tests. The puncture should not be deep enough to draw blood.

A small drop of the liquid allergen is ejected from the syringe onto the skin of the arm, forearm, or back and the puncture made through it by a rapid plunge of the syringe at such an angle as to facilitate penetration of the skin.

Stoesser[1] recommends three punctures for foods, two for inhalants, and one for pollens. Multiple punctures should be close together.

The preliminary drop of allergen may be dispensed with, especially when testing with pollens, as the author has found that the puncture itself will eject a sufficient quantity of the allergen into the skin to yield a positive reaction in cases where skin sensitizing antibodies to the allergen exist.

SUMMARY

1. An adapter for the allergy (Cooke) syringe is described which facilitates the performance of puncture skin tests.

2. The adapter, once attached to the barrel of the syringe, need not be removed. It does not interfere with the performance of intradermal tests.

3. The puncture technique of skin testing is a rapid, safe (minute quantities of allergen are used) and reliable method of testing and is especially suitable for the testing of children.

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REFERENCE

1. Stoesser, Albert A.: The interpretation of the allergy cutaneous tests. Journal-Lancet, 64:145, (May) 1944.

MANUAL OF ALLERGY LABORATORY AND DIAGNOSTIC PROCEDURES

The new revised edition of the Manual of Allergy Laboratory and Diagnostic Procedures is ready for the press and will be available by September 1. The old Manual has been completely revised and brought up to date. It will be bound in heavy buckram and will be much larger, giving all details for the making of allergenic extracts and their standardization, various diagnostic procedures and all details essential for the allergist who has his own laboratory for clinical and investigative use. Several hundred orders have been received for this revised edition, and those who have sent in their orders will be notified of details by post card as soon as the new Manual is available.

INDUSTRIAL DERMATITIS CONTROL

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INDUSTRIAL dermatitis is a subject of considerable interest to the allergist because of its compensation implications. Of the many allergic diseases in man this one can usually be supported by allergic proof.*

However, it is important to have a working knowledge of the common skin diseases, as these closely simulate eczematous dermatitis from external causes. Sulzberger enumerates some of the more common non-industrial dermatoses which must be considered in the differential diagnosis. These are seborrheic eczema, psoriasis, lichen planus, dermatitis herpetiformis, erythema multiformi, non-industrial fungus infections, impetigo, drug eruptions, herpetic impetigo, non-industrial dermatitis exfoliativa, atopic eczema, and non-industrial contact type dermatitis such as weed dermatitis.†

As far as industrial dermatitis is concerned, a knowledge of the locations in the factory where industrial sensitizers are located helps in the diagnosis of these. In our experience the greatest incidence of dermatitis occurs in those workers who are exposed to the chemicals used in the color processing of film and paper. At one time the incidence of dermatitis in these workers was as high as 75 per cent. At the present time this has been appreciably reduced so that it is less than 10 per cent. Methods of control have been accomplished by telling the workers the sources of the dermatitis and instructing them in the importance of the immediate neutralization of the chemicals by dipping hands in neutralizers as soon as they know that they have had an undue exposure to the chemicals. Washing of the hands with acid soaps instead of the alkaline soaps, using protective creams to protect the hands, as well as the wearing of rubber gloves when possible, is suggested.

Despite the above precautions some employes acquire dermatitis which usually subsides under treatment. The decision must then be made whether it is advisable to return these men to their former exposure or to another job. However, because of the phenomenon of hardening, which means the ability of the skin to build up a tolerance to chemicals formerly not tolerated, these patients can and do resume their former work. Such a practice is supported by evidence presented by Peck et al,** and is confirmed by our experience.

A word of caution should be added at this point. Care must be taken that the concentration of the chemicals which caused the dermatitis is not exceeded, as this will precipitate another episode of dermatitis.

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*Sulzberger: Dermatologic Allergy, page 87.
†Sulzberger: Dermatologic Allergy, page 467.
**S. M. Peck, et al: Industrial Med., 14:214, (March) 1945.

The hardening process is not permanent. Workers who are away from their jobs for a period of time, such as during illness or vacations, may again develop the dermatitis when re-exposed to their former job.

It is interesting to note that some patients never acquire a tolerance. These workers, of course, must be transferred to a job in which there is no chemical contact.

The control of dermatitis in industry is the combined responsibility of both the engineering and medical departments. It is, of course, the obligation of the latter to screen, first of all, new chemicals for their primary irritant and antigenic properties by patch testing guinea pigs. The next step is to observe the effects of these chemicals on the workers who are exposed to them. Obviously, chemicals of lower antigenic potential are substituted for those of higher potential wherever possible.

A most important factor in the control of dermatitis in industry is the selection of the man for the job. Workers with skin diseases, or with a history of allergy usually are ineligible for jobs which involve chemical exposure. This is because they are regarded as bad risks. Sulzberger summarizes the reasons as follows: "The existence of a non-industrial dermatosis may predispose to industrial dermatitis; and on the other hand industrial exposure may elicit attacks, prolong the course, or produce exacerbations of a non-industrial dermatosis."††

Education of employes must be undertaken concerning chemical sensitization so that they may avoid undue and prolonged exposure whenever possible. The hands may be protected with the use of protective creams, acid soaps, wearing of rubber gloves where needed, or by dipping hands in neutralizers after exposure to chemical sensitizers.

The most important step in the general treatment of industrial dermatoses is the removal of the patient from the chemical exposure which has precipitated the dermatitis. Attention is next directed to the control of itching because scratching may aggravate the dermatitis and increase the pruritus. The new antihistaminic drugs, Benadryl and Pyribenzamine, are the drugs of choice for the control of itching.

Following this, local treatment is instituted in the form of wet dressings, using solutions of potassium permanganate, aluminum acetate, or boric acid depending on the severity of the dermatitis. These, together with soothing lotions, such as tragacanth or calamine, and indicated ointments, comprise the treatment routine.

In addition the patient is cautioned to avoid skin irritants in his daily routine while at work or at home. The irritants to be avoided are soap and water bathing, paints, gasoline, shaving material, shampoo, nail polish, garden sprays, dusts, et cetera. One of the acid soaps is suggested as a substitute for the ordinary soaps.

Whenever a sensitized worker develops a dermatitis after a second exposure to a chemical with which he is working, the reaction in the skin

††Sulzberger: Dermatological Allergy, page 467.

does not stop at the moment that the antigenic contact is broken. In general, the patient's skin condition becomes worse before it subsides, regardless of the general or local measures carried out. It is important to inform these patients of this fact, not only that they may be reassured but also that they may not be disposed to lose confidence in the treatment and consequently seek other medical advice.

SUMMARY

The incidence of industrial dermatitis can be controlled by:

1. Skillful selection of men for jobs which involve chemical exposure. Eliminating those who have active or potential skin diseases.
2. Screening of new chemicals for irritant and antigenic properties by patch testing guinea pigs before exposing workers to them.
3. Substituting chemicals of lesser antigenic properties for those of greater antigenic potentialities whenever feasible.
4. Education of employes who are exposed to chemicals concerning chemical sensitization, so that they may avoid undue or prolonged exposure whenever possible, with emphasis on the use of protective creams, rubber gloves, and hand hygiene.
5. Seeking medical attention when the skin tolerance is exceeded.

NEOHETRAMINE IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS

(Continued from Page 319)

is indicated not only in human tuberculosis, but also in other infectious diseases, such as leprosy, which display important allergic components. Although experiments are in progress in our laboratories to confirm and extend our findings, it is hoped that this preliminary report will stimulate additional investigations in other laboratories.

SUMMARY

Neohetramine exerted a beneficial effect on the course of experimental tuberculosis in guinea pigs, although in the regimen employed it failed to influence the reaction to 1 mg. of Old Tuberculin administered intracutaneously.

1. Bernstein, T. B., and Feinberg, S. M.: J. Allergy, 19:393, 1948.
2. Boquet, A.: Inst. Past. Ann., *69:55, 1943.*
3. Breton, A.: Soc. Biol., C. R., 137:254, 1943
4. Criep, Leo H., and Aaron, T. H.: J. Allergy, 19:215, 1948.
5. Friedlaender, S., and Friedlaender, A. S.: J. Lab. & Clin. Med., 33:865, 1948.
6. Huth, E.: Z. ges. inn. Med., 3:65, 1948.
7. Sarber, R. W.: Am. Rev. Tuberc 67:504, 1948.
8. Scudi, J. V.; Reinhard, J. F., and Dreyer, N. B.: J. Allergy, 19:184, 1948.
9. Unpublished observations in laboratories of Nepera-Chemical Co., Inc.
10. Waldbott, Geo. L., and Borden, Robert: Ann. Allergy, 6:305, 1948.
11. Willis, H. S., and Jocz, T. R.: Nat. Tuberc. A. Tr., 34:125, 1938.

THE CLINICAL SIGNIFICANCE OF ACETYLCHOLINE

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EVIDENCE has gradually accumulated that acetylcholine is a factor in certain reactions which appear allergic. In discussing this evidence it is necessary to recall the normal functions of acetylcholine in the skin No attempt will be made to discuss the activities of this compound at motor nerve endings, at the synapses of peripheral ganglia or at synapses in the central nervous system, which are doubtless of vast clinical significance.

Most effects of stimulating the parasympathetic nervous system are caused by the release of acetylcholine at nerve terminals.[4,5] One of its characteristic effects is vasodilatation. Its local release at nerve terminals is probably the cause of vasodilatation in the skin, although the anatomical course of the responsible vasodilator fibers is in doubt. The sweat glands are innervated by fibers which, although anatomically running through the sympathetic system, liberate acetylcholine when stimulated. The flare about a histamine wheal is produced by an axon reflex running through sensory nerves and Wybaugh[23] has demonstrated release of acetylcholine at these sensory nerve terminals.

All the above activities of acetylcholine are potentiated by prostigmine and blocked by atropine and are among the muscarine-like effects of the drug. Recently Rothman and Coon[19] have shown that acetylcholine causes two interesting effects in the skin which can be produced also by nicotine. First, the intradermal injection of acetylcholine stimulates a contraction of the surrounding erector pilae muscles, producing the appearance of local goose flesh. This stimulus is carried through an axon arc localized in the skin and is effected by the liberation of sympathine at the terminals about the erector pilae muscles. The same investigators demonstrated in the zone surrounding an intradermal injection of acetylcholine that there was a stimulation of sweat glands again effectuated through an axon reflex arc, at the end of which acetylcholine is liberated. Perhaps of more significance, although less conclusive, is the evidence brought by Rothman and Coon[20] that acetylcholine is liberated in the wheal produced by histamine and is present in some inflammatory lesions of the skin.

These properties of acetylcholine are of interest because they throw light on the mechanism of some of the clinical phenomena called physical allergy.

Duke[7,8] introduced the term "physical allergy" to denote reactions resulting from heat, cold, light and mechanical stimuli. He reported instances of asthma, vasomotor rhinitis and conjunctivitis, photophobia, erythema, pruritus, eczema, abdominal pains and shock, but the majority of his cases were of urticaria with or without angioneurotic edema. He includes in this group factitious urticaria, the urticaria which occurs in certain indi-

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viduals on exposure to light, the urticarias produced by exposure to cold and those produced by exposure to heat. Among the heat-reacting cases Duke recognized two groups: one in which local application of heat produced wheals limited to the exposed areas, and another group in which anything which raised the body temperature, such as local or general exposure to heat or violent exercise, produced an outbreak of hives. In this second group similar outbreaks were caused by purely psychic stimuli.

Duke's descriptions of his cases were circumstantial and most of us could recognize among them examples parallelling cases in our own experience. The clinical phenomena were indistinguishable from those known to be caused by the chemical reaction of antigens and antibodies, but there seemed no tenable hypothesis as to how these physical agents could produce the same effect.

Since Duke's work, a number of observations have been made which point to mechanisms by which these purely physical stimuli may produce chemical effects without invoking any concept of the conversion of energy into matter. The similarity of the urticarial reactions to the histamine wheal made it probable that the wheals of physical allergy were like other wheals produced by the release of a histamine-like substance. Strong evidence in support of this was brought by Horton and Brown[15] who studied the gastric secretion of hydrochloric acid during outbreaks of urticaria from cold. There was a typical rise in secretion of hydrochloric acid during such attacks. The shock that occurs during severe outbreaks of cold urticaria also seems best explained by the release of a histamine-like substance. To this extent, then, the effects of physical stimuli seem mediated by a chemical agent. The hypothesis that light may cause lesions by acting on a photodynamic substance is generally accepted as explaining reactions which have followed injection of hematoporphyrin or those occurring in patients excreting uroporphyrin. Stein[21] reported that intradermal injection of serum from a case of hydroa estivale sensitized normal skin to light, and similar findings have been made in other forms of hypersensitivity to light.[3,17] Blum[2] and his associates have postulated the presence of a photodynamic substance to explain cases of urticaria solare in which passive transfer failed. None of these hypotheses invoke an allergic mechanism.

On the other hand, Gay Prieto,[16] Rajka[18] and, more recently, Sulzberger,[22] Baer and Blum[1] have succeeded in passive transfer of urticaria solare. The reaction in the passively sensitized skin was in these cases urticarial, which suggested an allergic mechanism. The hypothesis was advanced that light altered some tissue constituent, probably a protein, so as to give it antigenic properties. At least it has been shown in a number of instances that hypersensitivity to light is due to substances present in the blood serum.

Harris, Lewis and Vaughan[13] in studying cold urticaria found that it was of relatively frequent occurrence in congenital syphilitics with parox-

ysmal hemoglobinuria. By passive transfer of the serum from these patients they brought evidence of a dermatolytic antibody which combined with the cells of the skin at low temperature, just as the Donath-Landsteiner antibody united with red cells in the cold. By absorption of the sera with red cells of sheep they were able to remove the hemolytic but not the dermatolytic antibody, indicating that the two were distinct. This revealed one method by which physical stimuli could induce an antigen-antibody reaction with its ensuing allergic symptoms.

In 1936 Grant, Pearson and Comeau[11] published their studies on Duke's second type of heat urticaria. The spontaneous attacks in these patients occur after just those stimuli which release acetylcholine in the skin. Generalized attacks could be induced in these patients by subcutaneous injection of a stable analogue of acetylcholine. On skin test, reactions were produced by choline compounds analogous to the wheals produced in routine tests for allergy. These findings suggested another mechanism by which physical stimuli may produce allergic effects.

The hypotheses suggested to explain the mechanism by which physical stimuli act may be summarized as follows:

1. Light sensitivity might be explained by the presence of a photodynamic substance without assuming an immunological mechanism.
2. Proteins or other normal skin constituents might be altered by physical agents and act as allergens.
3. Acetylcholine released by physical stimuli might act as an allergen.
4. One physical agent (cold) may effectuate the reaction of an allergen and antibody already present.

In support of this last hypothesis we have a well-established analogy in paroxysmal hemoglobinuria and the passive transfer experiments of Lewis. The first three suggestions are hypothetical, but for the third there is much supporting evidence which warrants consideration.

Patients with generalized heat urticaria are familiar. They develop hives after hot baths, after violent exercise and also if they are excited or nervously upset. After a severe outbreak they fail to respond to any of these stimuli for a period which may be as long as twenty-four hours. The clinical appearance in these cases is almost diagnostic. The wheals are quite unlike those occurring in other types of urticaria. They are small and bead-like, rarely over 5 mm. in diameter, and are surrounded by brilliant flares 4 to 8 cm. in diameter. Cases are not infrequent which react to the same stimuli with these brilliant large flares and a variable degree of pruritus without producing any visible wheal. Nomland[16] has described patients subject to acute attacks of severe pruritus without wheals, in whom the attacks could be reproduced by Mecholyl.

Not all cases of psychogenic urticaria belong to this group. Patients who are not demonstrably sensitive to heat, some of whose attacks are due to known allergens such as food, occasionally have severe outbreaks from

psychic stimuli. It has been frequently claimed and seems fairly well established that hives can be induced in some individuals by suggestion. In such cases the wheals do not have the morphological character seen in typical cases of heat urticaria, and the mechanism of their production may well be different. The following observations probably do not apply to this group or to the group of persons described by Duke who develop local urticaria in areas exposed to heat.

The studies of Grant, Pearson and Comeau did much to elucidate the mechanism of generalized urticaria caused by heat. Experimentally, attacks may be induced by a number of procedures. If the entire body is placed in a hot cabinet, hives begin to appear as soon as the rectal temperature is increased from 0.4° to 1.2° F. They can be produced simply by wrapping the patient in a hot blanket or by making him exercise when heavily dressed. The most regular and marked response is obtained by heating one area—for example, placing one lower leg in a tub of hot water. When this is done, hives appear on all parts of the body except the immersed limb, which becomes profusely flushed. The absence of wheaing in the exposed area is probably because the increased superficial circulation in the limb rapidly carries away any H substance produced there.

If a cuff is placed above the heated area tight enough to occlude the venous return, the urticarial effect is not observed. If the cuff is released while the leg is still being warmed, urticaria appears after a short delay, but if the patient's leg is cooled before the cuff is released, no reaction occurs. This indicates that it is the warming of the blood transported from the immersed limb and not the addition to it of a chemical agent that produces the reaction. In one of Grant's experiments the forearm was congested by a cuff on the upper arm and the cuff then tightened sufficiently to occlude the arteries before the legs were placed in hot water. Bluish areas of vasodilatation were observed developing on the congested forearm, indicating a nerve and not a circulatory stimulus to this area. When the cuff was released and circulation restored, hives rapidly appeared at the spots of previous vasodilatation and elsewhere on the arm. In fact they were more numerous in the area distal to the cuff than on the other limbs or trunk and confluent in a band where the cuff had pressed. The intensified effect was probably due to something retained in the skin while the circulation was occluded. These experiments indicate the following course of events: Warm blood from the heated part is carried to some nerve center. From this center stimuli are sent out through the nerves to the areas in which hives develop.

That the development of hives was due to the release of acetylcholine was shown by Grant in two ways. If a solution of acetylcholine was placed under a negative electrode and a galvanic current passed through the body, a bright flare developed in the area under and around the electrode, and in the covered area a group of small round wheals frequently appeared. The effect could be more regularly produced if prostigmine were

added to the acetylcholine and carried into the skin at the same time, or if a more stable analogue such as acetyl-beta-methylcholine (Mecholyl) or carbominoylcholine chloride (Doryl) were used in iontophoresis. The reaction could be prevented by previous iontophoresis with atropine. They also showed that the subcutaneous injection of Doryl produced a general outbreak of typical hives in these patients, but not in normal individuals. Outbreaks could also be produced, as had previously been shown by Marchioninni and Ottenstein, by injections of pilocarpine. None of these effects could be produced in normal individuals or in those subject to urticaria from other causes.

Tests by intradermal injection give less convincing results but are of considerable interest.[14] Acetylcholine itself causes no distinctive reaction in these patients because of its quick destruction. Mecholyl or Doryl never produce spreading wheals with pseudopods like those produced by the common protein allergens. In a sensitive individual they cause a dome-shaped wheal perhaps larger than those produced in non-sensitized controls but not convincingly so. The most regular reaction in the hypersensitive patient is a wide flare. Frequently, in this flare a group of pinhead satellite wheals appear surrounding the large wheal produced by the injection. Their appearance suggests that the release of acetylcholine at the ends of the same reflex arcs which produce flares in normal individuals after injection of histamine, produces wheals in these individuals who are hypersensitive to acetylcholine.

Attempts to demonstrate an antibody in the serum of these patients by passive transfer have failed, and no attempts have been reported to induce allergy to acetylcholine. However, the hypothesis which would seem to explain these phenomena is that in the individuals concerned acetylcholine acts as an antigen or hapten, and that under any of the conditions which cause release of acetylcholine in the skin these hypersensitive individuals react by the secondary release of a histamine-like substance and the production of wheals.

The findings in this cholinogenic urticaria are of special interest because the reactions are produced not only by physical but by psychic stimuli.

Ever since Hippocrates, physicians have been impressed by evidence of the influence of mind on disease. The observed sequence of events often indicates that not only a subjective feeling of illness or a physiological reaction but actual chemical and structural changes in tissues have been caused by purely psychic stimuli. The apparent effects of such stimuli frequently mimic diseases which we consider allergic. A familiar example is allergic eczema. Patients who in infancy suffer from an eczema demonstrably due to their development of antibodies for specific foods often develop in adolescence a more chronic type of eczema. In some cases this is also an expression of food allergy. In other cases identical lesions seem to be caused by purely psychic disturbances.

The therapeutic successes of cults which treat disease only psychologi-

cally and the demonstrated effectiveness of psychotherapy are additional evidence of the psychic etiology of physical disease. This evidence has long been difficult to accept because no method has been demonstrated by which psychic stimuli could produce anatomical lesions. We seem to have a clue to the problem in the reactions of these patients with heat urticaria to acetylcholine.

The significance of acetylcholine may not be limited to this infrequent syndrome. It is interesting that Rothman and Coon[10] obtained reactions suggesting the presence of acetylcholine in fluid from lesions of allergic eczema and dermatitis herpetiformis—two diseases in which psychogenic factors are believed effective. Duke[9] noted functional cardiac disturbances in his heat-sensitive patients. Hall, Ettinger and Banting[12] were able to produce hyalin degeneration of the coronaries and myocardial degeneration or infarction in dogs by long repeated injections of this drug. In some young dogs similar doses caused hematemesis and melena. This again is evidence of the production of lesions by a chemical agent which is frequently released by psychic stimuli.

The character of the psychic stimuli which release acetylcholine has never been defined, but it may be possible to distinguish between adrenergic and cholinergic emotions. Two of Grant's patients developed lesions when stripped before a class for demonstration, others when they came to the laboratory for tests. One of our patients on whom we had made many gastric tests broke out at the sight of a stomach tube. One of Duke's cases had attacks when negotiating difficult business deals. Pleasant emotions have also been reported effective, e.g., watching an athletic contest (Duke) or anticipation of a dance (Grant). However, the effective emotions could usually be described as embarrassment, annoyance or apprehension. Cannon observed that pain, hunger, fear and rage in animals caused a discharge of adrenaline. He noted, however, that fear also stimulated the sacral parasympathetic. A reaction of defense was probably involved in the fear which he studied, whereas the milder apprehensions noted in our patients involved little such reaction. Diethelm and his associates[6] studied the effect on rabbit gut of blood withdrawn from patients under various emotional stresses. They concluded that anxiety, resentment and anger "are accompanied with definite adrenergic factors" and "tension and possibly fear with cholinergic effects."

The observations here reviewed are important as evidence of the clinical effects of physical and psychic stimuli. Any deductions drawn from them are uncertain. They indicate, however, lines of study that may clarify the mechanism of important psychosomatic reactions.

REFERENCES

1. Blum, H. F.; Baer, R. L., and Sulzberger, M. B.: Studies on hypersensitivity to light. II. Urticaria solare ($\lambda < 3700$). J. Invest. Dermat., 7:99, 1946.
2. Blum, H. F.; Barksdale, E. E., and Green, H. G.: Urticaria solare (λ4000-500A). J. Invest. Dermat., 7:109, 1946.

3. Callaway, J. L.: Passive transfer of light sensitivity. Arch. Dermat. & Syph., 51:889, 1940.
4. Dale, H. H.: Natural chemical stimulators. Edinburgh M. J., 45:361, 1938.
5. Dale, H. H.: Transmission of nervous effects by acetylcholine. Harvey Lectures. Baltimore: Williams and Wilkens, 1936-1937. P. 229.
6. Diethelm, O.; Doby, E. J., and Milhorat, A. T.: Emotions and adrenergic and cholinergic changes in the blood. Arch. Neurol. & Psychiat., 54:110, 1945.
7. Duke, W. W.: Physical allergy. J.A.M.A., 84:736, 1925.
8. Duke, W. W.: Heat and effort sensitiveness, cold sensitiveness. Arch. Int. Med., 45:206, 1930.
9. Duke, W. W.: Relationship of heat and effort sensitiveness and cold sensitiveness to functional cardiac disorders. J. Allergy, 4:38, 1933.
10. Gay Prieto, J.; Lopez de Azcona, J. M., and Azua Dochao, L.: Experimentelle Untersuchungen uber einen Fall von Urticaria Solaris. Arch. f. Dermat. u. Syph., 183:287, 1942.
11. Grant, R. T.; Pearson, R. S. B., and Comeau, W. J.: Observations on urticaria provoked by emotion, by exercise and by warming the body. Clin. Sc., 2:253, 1936.
12. Hall, G. E.; Ettinger, G. H., and Banting, F. G.: An experimental production of coronary thrombosis and myocardial failure. Canad. M. A. J., 34:9, 1936.
13. Harris, K. E.; Lewis, T., and Vaughan, J. M.: Hemoglobinuria and urticaria from cold. Heart, 14:305, 1928.
14. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria provoked by heat or by psychic stimuli. Arch. Dermat. & Syph., 38:679, 1938.
15. Horton, B. T., and Brown, G. B.: Histamine-like effects on gastric acidity due to cold. Proc. Staff Meet., Mayo Clinic, 7:367, 1932.
16. Nomland, R.: Cholinergic urticaria and pruritus. Arch. Dermat. & Syph., 50:247, 1944.
17. Rajka, E.: Discussion of presentation by E. Liebner: Licht urticaria. Zentralbl. f. Haut-u. Geschlechtskr., 34:405, 1930.
18. Rajka, E.: Passive transfer of light urticaria. J. Allergy, 13:327, 1942.
19. Rothman, S., and Coon, J. M.: Axon responses to acetylcholine. J. Invest. Dermat., 3:79, 1940.
20. Rothman, S., and Coon, J. M.: Studies on liberation of acetylcholine in the skin. J. Invest. Dermat., 3:99, 1940.
21. Stein, R. O.: Neue Befunde bei Hydroa Vacciniformis. Zentralbl. f. Haut-u. Geschlechtskr., 25:66, 1928.
22. Sulzberger, M. B., and Baer, R. L.: Studies in hypersensitivity to light. I. Preliminary report. J. Invest. Dermat., 6:345, 1945.
23. Wybaugh, L.: Transmission humorale de la vaso-dilatation. Comp. Rend. de la Soc. de Biol., 123:524, 1946.

A NEW ANTIHISTAMINIC COMPOUND FOR THE TREATMENT OF URTICARIA AND HAY FEVER

(Continued from Page 367)

patients who had received preseasonal and coseasonal injections of allergenic extracts.

4. Untoward side reactions were negligible.

REFERENCES

1. Lee, Henry M.; Dinwiddie, William G., and Chen, K. K.: The antihistamine action of N-(2-pyridyl)-N-(2-thenyl)-N', N'-dimethylethylenediamine hydrochloride. J. Pharmacol. & Exper. Therap., 90:83, (May) 1947.
2. Peirce, J. D., and Mothersill, M. H.: Treatment of allergic symptoms with a new antihistamine drug. J. Indiana M.A., 40:739, (August) 1947.

THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

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IT is the purpose of this report to review the literature on a new synthetic sympathominetic amine, -1-3'4' dehydroxy phenol -2- isopropylaminoethanol $(HO)_2C_6H_3CHOHCH_2NHCH(CH)_3$, named Isuprel, which is hailed by its investigators as a new and effective therapeutic drug in relieving the dyspnea of an asthmatic attack. It is also the purpose of this paper to discuss my experiences with this drug in a small series of cases.

It is claimed that Isuprel is a potent sympathetic amine which can elicit responses in the body similar to those of adrenaline, and that it has a pronounced broncho-dilator activity, a marked peripheral vasodilating action, and a good smooth-muscle relaxing ability.

From 1940 to 1946 several European investigators discussed the use of a drug known as Aleudrin which had the exact chemical formula as Isuprel. This Aleudrin was reported to be an effective anti-asthmatic when used as a simple spray. It was further claimed that the crises of experimental dyspnea induced in healthy subjects by the uses of choline aerosols could be controlled. R. Rosser and Dautrebande, Philippot, Charlier and Dumoulin also showed by their experimental work that Aleudrin could relieve the bronchial spasm induced by pilocarpine, ten times more rapidly than ephedrine.

In the U. S. the experimental work of M. S. Segal and J. F. Beakey with Isuprel[6,7] marks the first and only reports, as far as is known, on the drug. In this first report they analyzed the results of studies in eighty-two ambulatory patients with chronic bronchial asthma, and concluded that Isuprel was effective in relieving the dyspnea of bronchial asthma by three routes of administration, namely, oxygen aerosolization with doses of 1.0 c.c. of 1:100 dilution every three hours; subcutaneously with doses of .20 to .33 c.c. of 1:1000, and orally with doses of 30 to 90 mg. daily. They also showed that there was subjective relief from bronchospasm, together with improvement in the vital capacities and freedom of expectoration, as well as minimal undesirable pressor effects and tachycardia.

However, they cautioned as to reactions if more than 0.5 c.c. of 1:1000 was given subcutaneously and they suggested smaller doses on sensitive patients.

In their second and more comprehensive report on this drug, Segal and Beakey reiterated the results of their initial findings and included these additional findings:

1. The fluctuations in blood pressure in asthmatics, that is, the variation in the systolic and diastolic readings in inspiration and expiration were effectively abolished or markedly decreased, especially when the bronchospasm was greatest.

Doctor Lipman is an Associate Fellow of The American College of Allergists.

2. The epinephrine-fast state observed in eleven patients responded favorably with no fastness to Isuprel being observed.

It is the purpose of this report to discuss the office and home treatment of twenty-three ambulatory asthmatic patients with Isuprel. This paper is also concerned with a new route of administration—the sublingual, as well as the oral and subcutaneous routes. (As far as is known, no reports of results of treatment via the sublingual route have been made previously.)

My experience with Isuprel began in November of 1947. It was used in a series of twenty-three cases of bronchial asthma under treatment at my office and at patients' homes. The patients ranged from three and one-half to eighty-four years of age. Eight were males and fifteen females. These patients were currently under treatment for bronchial asthma, and some had been receiving either desensitization injections or various antihistaminics, ephedrine, the barbiturates, aminophylline or epinephrine at various times for the dyspnea of asthma. The desensitization injections on these patients were continued, but all drug treatment other than Isuprel was discontinued.

Each patient except the girl of three and one-half years was given a supply of Isuprel (5.0 mg. sublingual and 10 mg. Isuprel oral) with the instructions to dissolve the sublingual preparation under the tongue for each acute attack of wheezing and dyspnea. This was to be repeated once within thirty minutes if some relief was not obtained, and repeated again within fifteen to thirty minutes if any dyspnea persisted. Thereafter, one to two tablets (10 to 20 mg.) of the drug were to be taken orally every four hours. If insufficient relief was obtained, the patient was instructed to call me. The patient was then given .1 to .3 c.c. of Isuprel subcutaneously. The three and one-half-year-old girl was seen at home during two episodes of acute and very severe dyspnea of bronchial asthma which followed a severe cold. She was given .05 c.c. of Isuprel subcutaneously, with relief within five minutes on each occasion. Such relief lasted eight hours after the first injection of Isuprel, and after the second injection no further dyspnea was observed. The child was free of asthma for a period of about three months when last heard from.

The remaining results of treatment with Isuprel, together with the side reactions or complications, are tabulated in Tables I and II.

It will be observed that no attempt was made to determine the vital capacity changes or blood pressure fluctuations because of the inability to see all these patients immediately during their attacks and following the attacks. However, it was possible to observe the degree of relief obtained, as well as to determine the side reactions from the data presented by the patients themselves. In addition to the supply of the drug, the patient received a card of instructions requesting the following data: first, the severity of the asthmatic attack; second, the amount of relief obtained following the first, second and third doses—if such extra medication was

M.C.	55	F	11	Ephedrine and Amytal Adrenaline .5-1 c.c.	Slight relief for 30–60 min. and recurrence Relief—recurrence in 4–6 hrs.	None Severe weakness Nausea Vomiting Headaches	5 mg. Relief in 15 min. for 5 hrs. (2nd tab.) 5 mg. Relief in 15-20 min. less relief	60 gr. in 24 hrs. Slight relief only	2 c.c. Relief in 10 min. No recurrence	None
M.L.	68	F	27	Ephedrine Adrenaline 1 c.c.	No relief Taken frequently every day, 5–6x during acute attacks and relief few min. to 1 hr. States it is less effective than previously	Palpitation Faintness Nausea	5 mg. No relief in 20 min. 2nd tab. of 5 mg. Moderate relief. Severe palpitation and nausea		.15 c.c. Relief in 10 min. for 3–4 hrs.	Palpitation Faintness Dizziness
F.D.	76	M	30	Aminophylline 3½ gr. Adrenaline 1 c.c.	Relief for 2–3 hrs. No relief after first few yrs. of use.	None Palpitation Weakness Nausea Vomiting	1st tab. 5 mg. No relief in 20 min. 2nd tab. 5 mg. No relief	80 mg. in 24 hrs. Slight relief only	.2 c.c. Mod. relief. 32 c.c. Complete relief in 10 min.	Slight palpitation
E.N.	15	F	3	Tedral Adrenaline .5 to 1 c.c. Aminophylline intramuscularly 3½ gr.	Slight Good Fair	None Severe palpitation Weakness Vomiting Nausea Nausea and vomiting	1st 5 mg. tab. Mod. relief in 12 min. 2nd 5 mg. tab. No complete relief in 30 min. 3rd 5 mg. tab. Still some dyspnea		.1 c.c. Complete relief of dyspnea for 4 hrs. .15 c.c. Relief for 12 hrs.	Palpitation Faintness Palpitation for 15 min.
R.N.C.	64	F	15	Ephedrine ⅜ to ¾ gr. Adrenaline .5 to 1 c.c.	No relief Relief	Palpitation Palpitation Nausea Vomiting Diarrhea	1st 5 mg. tab. Partial relief in 10 min. 2nd 5 mg. in 30 min. More relief but some dyspnea	60 gr. in 24 hrs. Slight to mod. relief	.2 c.c. Relief prompt Relief in 10 min.	Mod. palpitation and nausea for 30 min. Severe palpitation and nausea for 10 min.
M.C.	32	F	4	Ephedrine Tedral Adrenaline .5 to 1 c.c.	Sl. relief Mod. relief Complete relief	None Palpitation Faintness Nausea	1st 5 mg. tab. Good relief in 10 min. for 2 hrs. 2nd tab. of 5 mg. Relief in 10–15 min.	60 gr. in 36 hrs. No further attacks.		Some palpitation after each dose

required; third, the follow-up relief with the oral tablets; and fourth, the list of side reactions or complications which they might have experienced.

TABLE II. SIDE REACTIONS FROM ISUPREL

	Sublingual	Oral	Subcutaneous
Palpitation	6	4	6
Weakness	1	2	3
Nausea	3	1	2
Vomiting	0	0	0
Headache or Throbbing	1	0	0
Nervousness	2	1	0
Sweating	0	0	0
Dizziness	0	0	1

SUMMARY

It will be noted that of the twenty-three patients treated, eight were males and fifteen females. Of these, twelve had a chronic type of asthma and ten, the paroxysmal type. The attacks of dyspnea varied from mild to severe, nine patients describing the attacks as mild to moderate and thirteen patients classifying them as severe. Out of the twenty-three cases treated, all used the sublingual tablets of Isuprel, nine the sublingual and oral tablets, and eight required sublingual, oral and subcutaneous treatments. Twelve patients out of the total were completely relieved of one or more attacks within five to thirty minutes by one 5 mg. tablet of Isuprel sublingually. In eleven, the relief persisted from one-half hour to several days at a time. Eight patients received only partial or slight relief from the first .5 mg. tablet sublingually and required one or more doses of the subcutaneous injections for complete relief. Two of the patients were not at all relieved by the sublingual and oral routes of treatment. Seven patients were kept comfortable and free from severe dyspnea by the use of oral tablets (after the initial relief with the sublingual Isuprel). Eight patients were relieved by the subcutaneous injections of Isuprel.

Out of the twenty-three patients, fourteen had side reactions ranging from mild palpitation to severe palpitation, weakness and nausea (Table II).

Of the seven patients receiving the subcutaneous injections of Isuprel, there were two who had been adrenaline-fast. The other five had had various side reactions after the use of adrenaline. Out of the twenty-three patients, five refused further treatment with Isuprel after three doses of the sublingual tablets, because of the side reactions, and four patients refused to continue the oral treatment for the same reason.

CONCLUSIONS

1. Isuprel sublingually is a good adjunct in the treatment of the dyspnea of bronchial asthma, although side reactions are common with its use.

2. Isuprel subcutaneously proved the most valuable drug of this group because its action was comparable to that of epinephrine and because it

(Continued on Page 440)

Reports in Brief

Papers appearing in this section were read By Title at the Fourth Annual Session, The American College of Allergists, held in New York City, March 12, 13, 14, 1948.

STANDARDIZATION PROCEDURE FOR DETERMINATION OF AEROSOL DELIVERY OF NEBULIZERS BY PHENOLSULFONPHTHALEIN AEROSOLS

Preliminary Report

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THE number of commercially available nebulizers for aerosol therapy of the lungs is increasing daily. Often exaggerated claims are made, both by the manufacturer and by the physician. It appears timely to propose that nebulizers be *certified* by the manufacturer to be capable of delivering a specified quantity of aerosol (not liquid) under standard operating conditions. In continuation of previous experiments we now propose the following procedure for the standardization and certification of nebulizers.[1]

1. Into the dry nebulizer, pipette 2 c.c. of 0.1 per cent phenolsulfonphthalein (PSP). Place small rubber stopper in air vent (if present) and attach the standard L-tube (DeVilbiss 640 L-tube), which acts as a one stage baffle, to mouth of nebulizer so that the L-tube is parallel to the table top.

2. Connect nebulizer to oxygen tank, or any suitable compressed gas with pressure tubing, and turn on oxygen. The tank is equipped with a gauge graduated in liters per minute. The time is counted from the moment the gauge reaches the required volume velocity, i.e., 8 1/m, et cetera, depending upon the construction of the nebulizer used. It is understood that this is an uncorrected volume velocity. A correction is not necessary for our present purpose.

3. After the gas has been allowed to run through for the desired time, usually five minutes, disconnect the rubber tubing from the nebulizer. Remove L-tube and wash out completely into a 50 c.c. volumetric flask, add 5 c.c. of 5 per cent NaOH. Bring volume up to 50 c.c. Determine colorimetrically.

4. The nebulizer is now washed out completely into a 500 c.c. volumetric flask. Five c.c. of 5 per cent NaOH is added, the volume brought to 500 c.c. and determined as for the L-tube.

From the Biological Laboratory, Cold Spring Harbor, New York, and the First Medical Service, and Laboratories of the Mount Sinai Hospital, New York City.

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TABLE I

RESULTS OF TYPICAL EXPERIMENTS ON NEBULIZER STANDARDIZATION

All nebulizers in this group were operated for 5 minutes with stopper and L-tube

	1	2	3	4	5	6	7	8	9
	Mg. Dye per c.c.	Type of Nebulizer	Initial Volume of PSP in c.c.	(Uncorrected) Volume Velocity of O_2 in L/m.	Residue in Nebulizer in mg.	Total Delivered in mg.	Baffled Quantity by L-tube in mg.	Per Cent Delivered	Ratio of Col. 7 to Col. 6 Per Cent
1.	1.04	DeVilbiss No. 40 (1)	2	6	1.43	0.65	0.13	31	20
2.	1.04	DeVilbiss No. 40 (2)	2	6	1.40	0.68	0.11	33	16
3.	1.03	DeVilbiss No. 40 (3)	2	6	1.30	0.76	0.13	37	17
4.	1.07	Vaponephrin (1)	2	5	1.34	0.80	0.004	37	0.5
5.	1.07	Parke-Davis Table Model	2	5	1.95	0.19	0.005	9	2.6
6.	1.07	DeVilbiss No. 44	2	4	1.97	0.17	0.00	8	0.0

The foregoing gives the following information:

1. Residue of dye in nebulizer itself.

2. Dye baffled out of L-tube. This is a rough value of "rain" plus larger particles subtracted from the original quantity by the nebulizer in addition to the L-tube deposit.

3. The initial quantity of dye in the nebulizer, minus the residue in the nebulizer, gives the total dye delivered by the nebulizer. This fraction holds in general for any solid dissolved substance.

The dye in the L-tube is a rough measure of the number of larger particles delivered. It is believed that the ratio:

$$\frac{\text{Dye in L-tube} \times 100}{\text{Total dye delivered}}$$

should not be greater than 35 per cent. However, the clinical importance of this ratio has not as yet been evaluated.

The important point emphasized by this report is that *aerosol delivery should be certified by the manufacturer of the nebulizers and that claims should be supported by acceptable laboratory evidence.*

Table I illustrates results obtained with this technique on four commercially available nebulizers. It should be emphasized that these data do not indicate in any fashion whatsoever which nebulizer is "the best" nebulizer. Sufficient data are not available to determine what particle size distribution is most desirable. The procedure and the table are designed to illustrate the way in which nebulizer delivery may be studied and standardized. Of the four nebulizers given in the table as examples, it is evident that the DeVilbiss No. 40 and the Vaponephrine nebulizers deliver sufficient mist to warrant their use with both epinephrine and penicillin under our conditions. On the other hand, there are many factors, which will be discussed in detail in a future communication, which determine, in

any particlular case, which nebulizer is to be preferred for clinical application. There are always restrictions attendant upon the use of certain nebulizers, e.g., where high volume velocities are involved. Certain nebulizers, for example, cannot be used efficiently with high volume velocities which are desirable with nasal tips. Other nebulizers are very efficient with low volume velocities. It has been pointed out previously that 10 liters per minute is desirable with nasal tips. In addition, the particle size distribution, as determined by the quantity baffled by the L-tube (Column 7), makes it appear likely that wider range of particle distribution, and thus clinical effectiveness, might be made available by nebulizers which provide from 10 to 50 per cent of the mist delivered in particles large enough to be baffled by the L-tube.

Comparison of dye and penicillin aerosol excretion in man are experiments now in progress.

SUMMARY

By nebulizing a solution of a standard dye, under specific conditions, the quantitative delivery of aerosols by commercial nebulizers may be readily determined. It is recommended that commercial nebulizers be certified as to aerosol delivery by the manufacturer.

REFERENCES

1. Abramson, H. A.: Principles and practice of aerosol therapy of the lungs and bronchi. Ann. Allergy, 4:440, 1946.
2. Abramson, H. A.: Present status of allergy. The Nervous Child, 7:86, 1948.

THE USE OF ORAL POTASSIUM TREATMENT IN ATOPIC DERMATITIS

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THIS report is based on the clinical observation that a number of patients presenting the syndromes of both bronchial asthma and atopic eczema showed improvement of the dermatological condition when given potassium iodide orally for the chest symptoms; a group of patients with typical atopic eczema alone was so treated. Each was given a saturated solution of potassium iodide by mouth; and no other treatment, topical or otherwise, was instituted. In three patients who were hospitalized for this study, immediate marked improvement occurred. Change of environment may have played some part, although one individual has maintained his complete remission while at home. One patient, not hospitalized and given no other treatment, has been in remission for fourteen months.

The study is being extended to a public clinic and to the laboratory in order to establish such causal relationship as may be present.

A STUDY OF ONE HUNDRED ALLERGIC INDIVIDUALS BY THE MINNESOTA MULTIPHASIC PERSONALITY INVENTORY TEST

ETHAN ALLAN BROWN, M.D., F.A.C.A., I. ALAN ANNIS, M.D., and LIONEL P. GOITEN, M.D.
Boston, Massachusetts

ONE hundred patients, seen in a public allergy clinic, were studied by means of the Minnesota Multiphasic Personality Inventory Test. The allergic syndromes were limited to hay fever, bronchial asthma, or both.

Eleven patients demonstrated hypochondriasis. In one of these, the personality trait was associated with hysteria and in two others there were, as well, traits of hysteria and also depression. In one, the hypochondriasis was associated with traits of sexual inversion. Five female patients presented high scores for masculinity; and one male, a high score for femininity. Four patients showed marked scores for depression and five for hysteria. Two demonstrated psychasthenia, one schizophrenia, and one hypomania. Fully one third of the patients were obviously psychoneurotic.

AN EVALUATION OF ROUTINE X-RAY STUDIES IN ASTHMATIC PATIENTS

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ROUTINE chest and sinus x-rays were done on 450 consecutive patients presenting bronchial asthma as their chief symptom. Of the 220 completely evaluated, approximately thirty showed both systems to be normal. Of the others, fifty-six presented mild emphysema, which was moderate in an additional 104, and marked in thirty-three. Evidence of bronchitis was mild in ninety-four, moderate in eighty-four, and marked in nineteen. Hilus shadows were slight in eighty-one, moderate in eighty-six, and marked in twenty-two. Thickened sinus membranes were reported slight in eighty-nine, moderate in fifty-six, and marked in forty-four.

For other conditions, tuberculosis was present in sixteen, bronchiectasis in nine, atelectatic patches, four; emphysematous blebs, two; cervical ribs, three; tracheal deviation, sixteen; enlarged left ventricle, five; and sclerotic aorta, sixteen. Other pathological conditions were present in very small numbers. In nineteen patients polypi were diagnosed by x-ray. Incidental diagnostic findings were: three patients with neoplasms and three with Paget's disease.

The final report will be presented when a total of 500 patients similarly studied has been evaluated.

A DURHAM-TYPE AIR-SAMPLING DEVICE FOR LESS THAN ONE DOLLAR

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Flint, Michigan

THE stainless steel air-sampling device as described by O. C. Durham (J. Allergy, 17:79, 1946) costs in the neighborhood of $20.00. A simple, equally effective air-sampling device (Fig. 1) can be made by the use of

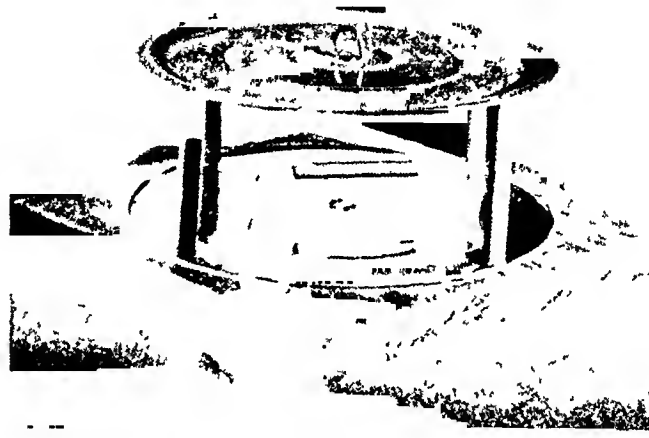

Fig. 1. Inexpensive Durham-type air-sampling device.

two aluminum pot lids, four pieces of ½ inch diameter doweling for posts, and a wall hook bent to serve as a slide holder. A crate end or any piece of board can serve as a base.

Cost of materials: slightly less than one dollar.

Construction time: forty-five minutes to one hour.

AEROSOL PENICILLIN IN ALLERGIC PATIENTS WITH RESPIRATORY INFECTIONS

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AEROSOL penicillin was administered as an adjuvant therapeutic office measure in the ambulatory management of allergic patients with acute and chronic diseases of the upper and lower respiratory tracts.

Over 200 aerosol treatments were given to seventy-nine patients with respiratory allergies, complicated by secondary infection of the respiratory tract. In forty-two of these patients, the underlying major allergy was bronchial asthma; eight patients had hay fever, and twenty-nine had allergic rhinitis.

Description of the technique employed is included.

Emphasis is made of the simple and readily adaptable procedure in all age groups, the paucity of side effects, and its possible role in limiting the course of secondary respiratory infections in allergic patients.

Also included is a table of the patients receiving the treatment, showing the effect of aerosol penicillin on the vital capacity, sedimentation rate, et cetera.

It is felt that the presentation of additional clinical data is desirable pertaining to the use of aerosol penicillin in allergic patients.

COCCIDIOIDOMYCOSIS TREATMENT WITH HISTAMINE

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COCCIDIOIDOMYCOSIS was first described in 1892. In 1937 it received recognition as being endemic in certain areas of California, Arizona, Texas and possibly a few other dry climates, caused by the diphasic fungus coccidioides immitis. There are two types: (1) simple or initial, (2) progressive, secondary, disseminating—usually fatal. One case in 500 is of the disseminating type, known as coccidioidal granuloma. The condition produces a high metabolic rate, eosinophilia, and other allergic symptoms —especially those produced by large amounts of histamine or histamine-like substances. Treatment has been immunologic therapy. Histamine was used intravenously and subcutaneously, in one case, to build up histamine tolerance with rapid subsiding of clinical symptoms and apparent cure. There is no record in the literature of histamine's being given intravenously in a case of progressive coccidioidomycosis before.

MASSIVE SPONTANEOUS SUBCUTANEOUS EMPHYSEMA OCCURRING IN AN ASTHMATIC ATTACK

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THE spontaneous occurrence of subcutaneous emphysema is an uncommon phenomenon. A review of the literature reveals only twenty-one previously reported cases, of which several had a concomitant pneumothorax.

The two cases reported in this paper occurred in young, vigorous males who had been having infrequent attacks of asthma for several years.

In both cases there were no warning signs or symptoms. During an acute asthmatic siezure, the patients noted puffiness of the neck which cracked on palpation. In one instance this swelling extended over the entire right chest and abdomen down to the inguinal ligament. During

treatment, consideration was given to multiple skin punctures and insertion of drains. However, in neither case was the patient excessively dyspneic; and, as both patients responded to conservative measures, they were treated expectantly. The emphysema absorbed completely in both instances, in ten and fourteen days.

An interesting feature about one of these cases is the path taken by the air from the ruptured vesicle in the peripheral lung, along the walls of the bronchioles and the blood vessels, into the middle mediastinum—causing a shift of the heart to the left—thence along the facial planes to the neck, and finally subcutaneously down the chest and abdomen to the inguinal ligament.

Spontaneous subcutaneous emphysema may occur more frequently than reported, but because the syndrome is asymptomatic it is probably overlooked.

"CEREBRAL EDEMA" DUE TO PHENOBARBITAL SENSITIVITY

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3. Criep, L. H.: Essentials of Allergy. P. 278. Philadelphia: J. B. Lippincott Co., 1945.
4. Hansen-Pruss, O. C., and Leeper, Jr., W. E.: Methods for the objective demonstration of suspected drug sensitivity. Ann. Allergy, 5:541-545, (Nov.-Dec.) 1947.
5. Herman, N. B.: Drug allergy. Clinics, 5:571, (Aug.) 1946.
6. Hueber, E.: Ein Fall von Luminalvergiftung mit todlichem Ausgang. Munchen. med. Wchnschr., 66:1090, 1919.
7. Kennedy, Foster: The allergic influence in migraine and some other allergic manifestations in the nervous system. Fall Graduate Instructional Course, American College of Allergists, Cincinnati, 1947.
8. Landsteiner, K.: The Specificity of Serological Reactions. Springfield, Ill.: Charles C Thomas, 1936.
9. Poole, K. A., and Wehger, R. T.: Fatalities in exfoliative dermatitis. J.A.M.A., 102:745, (March 10) 1934.
10. Ratner, Bret: Allergy to drugs and antibiotics. Fall graduate instructional course, American College of Allergists, Philadelphia, 1946.
11. Sulzberger, M. B., and Baer, Rudolf L.: Office Immunology. P. 290. Chicago: Year Book Publishers, Inc., 1947.
12. Urbach, Erich., and Gottlieb, Philip M.: Allergy, 2nd ed., p. 318. New York: Grune and Stratton, Inc., 1946.
13. Vaughan, W. T.: Allergic migraine. J.A.M.A., 88:1383, 1927.
14. Winer, Nahum J., and Baer, Rudolf L.: Exfoliative dermatitis due to phenobarbital. Arch. Dermat. & Syph., 43:473-484, 1941.
15. Zeller, M.: Penicillin urticaria. Ann. Allergy, 3:360, (Sept.-Oct.) 1945.

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Progress in Allergy

BRONCHIAL ASTHMA V

Critical Review of Literature

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Chicago, Illinois

We have again attempted to cover the literature on asthma and related conditions, this time from July 1, 1947 to September 30, 1948. In addition, a few articles of earlier dates are included because they were not mentioned in our first four reviews of the literature of 1943,[518] 1944,[519] 1945,[520] and 1946-June 30, 1947.[521]

Antihistaminic drugs are increasing in number, with many articles. A healthy sign, too, is a revival of the study of physiological and pharmacological aspects of the respiratory tract. Psychological factors seem to draw more and more attention. Reports from military sources are now very few.

The study of allergy has spread to many countries. Allergy societies continue to increase in this country and many new ones have been formed in other countries. This increased popularity has stimulated a large number of articles written in foreign languages. We have been fortunate in obtaining expert assistance in studying many of these, and we here wish to acknowledge, with gratitude, help received from Drs. Carlos Tanturi (Argentina), Gonza Estrada De La Riva, (Havana, Cuba), Jacques Sclafer (Paris, France), and Arnold Schimberg and H. Blackburn (Chicago). Once again we beg those who write in languages other than English to end their articles with a summary in English. This summary should not merely discuss the subject matter; it should give facts and figures wherever possible. In return, those of us who write in English should reciprocate. We again ask for reprints on asthma and related subjects, with translations or abstracts of all foreign papers, so that we can include them in our next review.

NEW BOOKS

New books have been few and none deal with asthma alone. "Synopsis of Allergy," by Alexander,[16] second edition, presents the essentials of allergy in a compact form, and includes excellent chapters on bronchial asthma, allergic dermatoses, and allergy to drugs and chemicals. Drawbacks exist, e.g., the belittling of skin tests and the complete acceptance of the unproved theory that contact between a specific antibody "and the atopen causes the release of histamine (H-substance)."

Another second edition is on "Physiologic Therapy in Respiratory Diseases." Barach has done well and "correlates the pathologic physiology of each disease entity with the physiologic principles which underlie the treatment of the condition by inhalation therapy and other procedures which have value in the management of respiratory diseases."[49]

Black's revision of Vaughan's "Practice of Allergy" is a "must" in this field. However, as stated in a review, the book remains Vaughan's, for the most part, with relatively little new information by the new author, and with only a few recent references in spite of many new articles and books on the subject.[533]

"Office Immunology Including Allergy," by Sulzberger and Baer, along with four other authors, is excellent, although, as expected, there is much more discussion of dermatologic allergy than that of the respiratory tract.[500]

Kern[279] has a book on "Perennial Allergic Rhinitis: the Most Important Respiratory Allergy."

Forman[161] has compiled a very useful "Directory of Physicians Interested in Clinical Allergy." The names are listed by states, cities and countries, with brief data concerning membership in professional societies.

We recommend four books on fungi. They are Henrici's "Molds, Yeasts and Actinomycetes" (second edition and revised by Skinner, Emmons and Tsuchiya);[252] Nickerson's "Biology of Pathogenic Fungi";[359] "Fungi of Manitoba and Saskatchewan" by Bisby and others;[66] and "The Fungi" by Wolf and Wolf.[563]

ETIOLOGY OF BRONCHIAL ASTHMA

Alford[18] has an interesting paper on allergy in Japan. In contrast to the United States, grasses and ragweeds are unimportant; hyposensitization is practiced only in

the medical schools. All sorts of nonspecific measures are used, some good, some useless. There are no active allergy clinics. House dust is of little importance in Japan because "a typical Japanese living room has no drapes, rugs, pillows, upholstered furniture or animal pets. These rooms thus approach our concept of a dust-free environment. The bedrooms do not have beds or mattresses. Cotton quilts are placed on the floor and the small pillows are frequently of straw. During the daytime these quilts are folded up and placed in bureau drawers or cupboards. There is usually considerable air circulating through the houses due to their construction and thus house dust cannot accumulate easily." Asthma does occur in Japan, with one case due to inhalation of silk worm cocoon, and others to various foods and especially to Ascaris infestation. As in South America, sensitivity to foods seems much more important than to inhalants, although mold allergy is frequent. Urticaria, especially to various sea foods, is the most common allergic condition in Japan. The Japanese are not racially immune to hay fever even though hay fever does not seem to exist in Japan.

In Norway about 700 persons are totally disabled as a result of bronchial asthma. Claussen[110] surveyed 86 of the 377 districts. There were 1,190 asthmatic persons among the 295,356 inhabitants in those districts. From these figures, he estimates at least 12,000 persons with asthma in all Norway (population about three million). Like other observers he found more male patients (58 per cent). In the first decade there were only thirty-four girls to every sixty-six boys, and in the second decade boys constituted 69 per cent. In over fifty cases the asthma had lasted over forty-five years. There was no great difference in the frequency of asthma in coastal and interior districts. Complete disability occurred in 7.3 per cent of the men with an average age of fifty-three years and an average duration of the disease of eighteen years. Only 4.5 per cent of the women were completely invalided. The family history was positive in 50 per cent, with onset of asthma earlier in those with positive history. Asthma is a national scourge.

POLLEN

Pollen as a cause of hay fever and asthma continues to draw attention. By using two simple sampling devices Durham tested the allergen-producing ability of more than sixty plant species and several fungi. As a result of repeated spot testing of the air in the immediate vicinity of single plants, small plots or extensive acreages, he obtained some extraordinarily high counts, especially high when compared with maximum gravity data (stated on volumetric basis), as previously reported for these plants in areas where they are most abundant. For example, a spot count of 9,600,000 ragweed pollen was found in a visible cloud twenty feet from the weeds themselves. Other high spot counts were 160,000 for burweed marsh elder (iva xanthiifolia), 2,000,000 orchard grass, 460,800 Canada blue grass, and 328,000 redtop.[365] Such extreme figures emphasize the fact that occasionally one or a few plants can cause hay fever or asthma in a person who happens to be close by.

Durham[163] found that some of our National Parks are entirely ragweed-free; some contain ragweed in season, e.g. near Mammoth Cave, Kentucky. Durham and his collaborators of the American Academy of Allergy[164] give the 1947 ragweed pollen counts from fifty-eight different locations in various parts of the country. The totals range from nine in Grand Canyon, Arizona, to the high counts customary in the midwest, especially in Decatur and Peoria, Illinois. Walzer and his co-workers[650] surveyed New York City and its metropolitan area. In 1946 the seasonal pollen totals were uniformly low; that for Brooklyn was only 48 per cent of the average for the past eleven years. During this same year totals for Washington, D. C., Philadelphia and Cleveland were two to five times the average total for New York City.

Stroh,[499] in the Northwest, states that the Cascade Mountain range divides this area into two distinct regions with different climates and pollens. West of this range the weather is similar from Northern California to Juneau, Alaska, with tree pollen in February and March. Grasses begin in April and reach their maximum in June. There is no true fall season. East of the range the flora is typically midwestern with slightly later tree and grass seasons; the fall season is most important (Russian thistle and sagebrush, especially).

Ordman,[203] in South Africa, found that symptoms occurring in the summer are almost invariably due to grass pollen (October to March.) Tree pollenosis is uncommon, but hay fever in spring and winter is usually due to the pollen of the Cypress tree. Weeds are of little significance though *Compositae* (especially common garden flowers) can cause symptoms. Alemany-Vall[12] found grasses most important—there are ninety-seven species within the municipal boundaries of Barcelona, Spain, from March to July; the pollen of *Parietaria Officinalis* is a frequent cause of simple and complicated rhinitis and asthma.

Veldee[335] discusses the qualifications of the pollen collector, the labeling and type of containers, the purity and stability of the pollen, change of color in dried pollen, and the necessary co-operation between the user and the collector of the pollen. The New York City Health Department destroyed more than 1,000 acres of ragweed by spraying with a chemical which kills the weed before pollen is set free.[337] Ragweed hay fever does not occur in Europe, although a few ragweeds are found in local areas.[33] Filters protect against pollen hay fever but those whose asthma is due to pollen usually do not clear up until they have been in an air-filtered room for from one to several days.[24]

FUNGI

The role of fungi as a cause of rhinitis and asthma is now well established. Durham[105] did counts of both fungi and pollens. His highest natural Alternaria count was 13,600 in Illinois, but from a heavy cloud of dust produced by an operating combine he obtained spot counts of 675,000 Alternaria, 869,000 Hormodendrum, and 177,327 Helminthosporium. In another spot count he found 500,000 corn smut. These terrific figures prove what we have known clinically and by skin tests—that certain molds and smuts can and do cause respiratory symptoms in many individuals.

Eisenstadt,[172] in a study of 380 cases of respiratory allergy, ages two to sixty-four, tested with eight different 1:1000 mold extracts. Positive reactions were obtained in 129 cases (34 per cent.) Inhalation of one or more molds was the main cause of the respiratory allergy in forty-two patients (11 per cent), and a contributory factor in another sixty-nine cases (18 per cent)—total 29 per cent. Alternaria and Hormodendrum were of major importance, both in relation to mold spore counts and to frequency of positive skin tests. Other molds may also be of clinical significance, and the author rightly urges routine testing with mold extracts in all patients with asthma and rhinitis, including hay fever. On two occasions constitutional reactions occurred after intradermal testing. [These reactions which could have been serious, even fatal, emphasize the necessity for doing preliminary skin tests by the scratch method. Besides, scratch positive reactions with mold extracts are almost always associated with clinical sensitivity. This is by no means true with the intradermal technique. Eisenstadt, for example, in this paper obtained positive intradermal skin tests to molds in eighteen patients in whom there was no clinical significance].

Morrow[350] made another survey of thirty-one stations in the United States for periods up to six years. By the mold culture plate technique the following molds were the "top ten:" Alternaria, Hormodendrum, Penicillium, Aspergillus, Pullularia, a sterile pale species, sterile dark species, Torula, Fusarium, and Trichoderma. In January and March by the plate method only, Newton, Scherago and Weaver surveyed parts of Kentucky. Penicillium was the most prevalent mold in all parts of the state. They found four genera, *Montospora, Stemphylium, Tetraccocosporium,* and *Phycomyces,* not previously reported in Kentucky. Certain molds predominated in outdoor air and others in house dust; mold surveys should therefore include house dust as well as outdoor air.[358]

From West Texas, in a five-year survey, Sellers and McKenzie[456] made intradermal tests with eight mold extracts in 392 sufferers from inhalant allergy. Thirty-three patients (8.4 per cent gave positive tests only to molds, and another 141 (35.9 per cent) were positive for molds and other inhalants. Mold sensitivity was especially common in patients under twenty. Specific treatment was successful in twenty-one of the thirty-three patients sensitive only to molds and in 49.4 per cent of those patients who were allergic to molds and other inhalants. Molds are present throughout the year in the Abilene area of Texas (slides and plates).

From Copenhagen, Denmark, Flensborg and Samsoe-Jensen[153] surveyed the outside air from March to September, 1947: the mold spore counts were very high, especially during the summer; Hormodendrum was most important, especially in and after June, reaching 80-120 colonies daily most of this time, with a peak of 260 one week in July. This mold accounted for 72.4 per cent of all molds, with Penicillium 9.2 per cent, Monilia 2.4 per cent, Pullularia 2.2 per cent, and Alternaria 2 per cent. In a study of the homes a different situation was found—various species of Penicillium were present and only occasionally Hormodendrum. In discussing this paper, Nilsby, from Sweden, agreed that Hormodendrum was far more prevalent than Penicillium in outdoor air, but Penicillium was found indoors in 43.5 per cent, Hormodendrum in 27.5 per cent, Yeast-like structures in 10 per cent, Aspergillus in 6.2 per cent, and Alternaria in 2.1 per cent. Molds may differ in different homes. In one home, there was a pure culture (25 colonies) of Alternaria, a mold rather rare in Sweden. Schwartz of Copenhagen cultured the house dust of twenty-two asthmatic patients (plate exposures). He found a total of 239 fungi with a great predominance of

Penicillium, followed by Aspergilli, Mucor and the others. In one home there were seven different varieties of Penicillium yet only one of these gave a good intradermal test on the patient.

Two methods of preventing mold growth on books are offered. One is to maintain humidity below 75 per cent in a book case by open bags containing silicagel, the other by wiping the bindings with a solution containing thymol, mercury bichloride, ether and benzene.[130] Cavallero has a long review of allergic diseases due to fungi.[105]

Dutton[167] believes that a patient can be sensitive to fungi present in his own bronchi. For twelve years he has studied sputum of asthmatic patients, both by the usual stains and by culture. In a small percentage, non-pathogenic fungi of various kinds have been found and extracts of these fungi have given excellent scratch, intradermal, and transfer reactions in some of these patients, with clinical improvement by hyposensitization. By this technique a small but significant number of patients has been definitely benefited. A few in this group showed no other sensitivity nor other factors to explain their asthma, and for them the results have been striking.

HOUSE DUST

Three excellent papers come from a group in London. Rimington, Stillwell and Maunsell[418] obtain their dust for extraction from a single dust supply, chiefly from carpets. The crude house dust extract is prepared by soaking in ammonia, squeezing out the extract, followed by re-extraction and filtering through Kieselguhr. The completed extract contains 2-3 per cent nitrogen and is used for testing in a 1 per cent solution. The authors state that their method gives stronger intradermal reactions in house dust-sensitive patients than do Seitz-filtered fractions. In the second paper[497] the authors compared the reactions given by allergic individuals to purified house dust antigens, the pooled extracts of twenty-six strains of molds grown in pure cultures, the culture fluid obtained from the latter, and materials predominately polysaccharide in character isolated from four species of Penicillium and one species of Caldariomyces. All these mold extracts gave negative intradermal tests in nonallergic persons. In sixty-two patients with allergic rhinitis, tests for the house dust extract were positive in forty-five; of these, fifteen were also positive for the mold extracts. All seventeen patients who were skin-negative for dust were also skin-negative for molds; no patient showed a sensitivity to molds and an insensitivity for house dust. There was a striking chemical similarity between the three polysaccharide products derived from the molds after hydrolysis and the dust antigen. All showed polypeptide-like grouping of simple amino acids associated with a polysaccharide complex. The usual color reactions for protein were not obtained.

In the third paper[366] their crude dust antigen (10 mg. to 10 cc. normal saline plus 0.5 per cent phenol) was diluted serially to 10^{-4}, 10^{-5}, and 10^{-6} concentrations. Of forty-nine nonallergic persons none gave threshold reactions with the 10^{-6} dilution, three reacted to 10^{-5}, and seventeen to 10^{-4}. Negative reactions were obtained in twenty-nine (58 per cent) of normals to 10^{-4}, whereas 90 per cent of ten persons with a history of allergy reacted to this dilution, and four of these to 10^{-6}. Positive tests to 10^{-5} were obtained in fifty-five of eighty allergic patients. In a group of thirty-five positive-dust-reactors twenty-two also gave positive tests to extracts of cats, feathers and/or molds. No patient reacted to one of these latter three and failed to give a positive test for house dust extract. After hyposensitization there was a decrease of the threshold reactivity to the dust extract but a blocking antibody was not found in the blood of those patients. [The authors could have obtained a much stronger dust extract by discarding rug and carpet dust; dust from bedding and soft furniture is much more potent.]

That molds are important in house dust, but not the entire story, has also been shown by Reymann and Schwartz.[410] (Also see discussion above of paper by Flensborg.) From the dust obtained from the homes of twenty-two asthmatic patients, 239 fungi were cultured and six of these patients gave positive skin tests to those molds when extracted. Those who were mold-sensitive also gave positive skin tests for house dust but the reverse was not always true. Of these twenty-two patients thirteen gave positive tests for their "autogenous" house dust extract, and five of these also gave positive skin tests for the fungi present in their own dust. Blamoutier[72] discusses the house dust problem as a cause of asthma and the origin and nature of the dust. He is very skeptical as to results of specific hyposensitization. [This skepticism is not shared by most American allergists. We know that we obtain excellent results in most cases of dust-sensitive respiratory allergy; we combine rigid elimination of inhalation plus hyposensitization. We admit that we do not know what per cent of improvement is due to the injections alone, but, by analogy with results in those who receive injections of extracts of horse dander, molds and pollens, we feel

that hyposensitization is an important and useful procedure, and we therefore do not share his skepticism.] An answer to a query[25] correctly states that "generally a stock dust preparation made by obtaining house dust from a number of homes, preferably of patients with respiratory allergy, is satisfactory in the majority of cases of sensitivity to house dust. There are occasional patients in whom a preparation made from the dust of the individual's own home ("autogenous") gives better reactions than the stock dust preparation. This may be due to a relatively excessive amount of one or more of the allergens in the preparation to which the patient is selectively more sensitive," e.g. feathers or kapok. [It should also be pointed out that, as stated above, a particular house dust may contain one or more molds to which a patient may be specifically allergic.]

INHALATION OF FLOUR AND GRAIN MILL DUSTS

Jiménez-Díaz and his associates[272] from Madrid confirm previous reports that cereal dust contains more than one ingredient. In order of importance they place fungi, insects, acarina, and substances in the dust and flour itself. The most important fungi are rusts, smuts and Tilletia; these are found in great quantities in granary dust and that of milling establishments, owing to their fineness and the ease with which they spread once the covering of the invaded grain has been broken. The infected grain, equally with Ustilago and Puccinia, can spread in the air when the seeds fall and may affect neighboring people. Other fungi, e.g. Aspergillus and Penicillium, can invade damp flour, but much less often. Cases are noted of sensitivity to tricoptera (Caddis fly,) ephemerida, Musca domestica, and Climex lectularius. Coleoptera can cause symptoms in mill workers or in those close by, while sensitization to the flour itself is of most importance in bakers. In twenty-four cases, especially with sensitivity to Tilletia (main cause of asthma in mill workers and others exposed to grain in Spain,) positive skin tests were obtained and positive passive transfer in fourteen Tilletia cases. On the other hand, only two positive transfer reactions were found to the flour itself.

Four other papers discuss allergy in bakers. Linko[302] from Finland, examined 328 workers and found sixty-six (20 per cent) with clinical allergy to flour. Forty had only nasal symptoms, twenty both nasal and asthmatic trouble, and only six asthma alone. Blood eosinophilia was found in nineteen, with positive skin tests to cereal extracts in 60 per cent. Family predisposition did not seem important. Onset of symptoms averaged eleven years after entering the profession, with earlier onset in thirty-two cases. Schwartz, from Copenhagen, found thirty-five persons with flour allergy (twenty-four bakers, two millers, seven confectioners, one worker in a biscuit factory, and a miller's son.)[118] The average sensitization time was under eleven years. Specific desensitization with flour extracts led to improvement in only 38 per cent of cases. Schwartz has an excellent discussion of flour allergy; it is an occupational disease and therefore prophylaxis is important. This includes (a) lessening of the amount of dust in bakery shops by better ventilation; (b) avoidance of this occupation by allergic individuals; and (c) he points out that some bakers can become confectioners because of less flour dust. In Denmark for the period 1928-42, inclusive, 1,654 persons received an invalid pension because of asthma; of these only fifteen were bakers, confectioners or millers, a very low percentage. Eight of the above thirty-five patients quit bakery work, seven of these had not been helped by hyposensitization.) Seven of these men became symptom-free within three months but all receive lower wages in other trades. One is disabled with bronchiectasis. It is interesting to note that these flours were examined microscopically and were free from mites and other insects, and that injections were given for from six weeks up to four months. [This confirms our impression of the difficulty in clearing baker's asthma while the patient remains exposed to large amounts of flour. Housewives are less exposed and usually get excellent results even when they inhale some flour dust at intervals.]

Alemany-Vall (Madrid)[11] also discusses asthma and rhinitis due to flour. The appearance of eosinophilia in the nasal or bronchial secretions seems to be a prelude to attacks. From South Africa, Ordman[367] says that wheat was recently lacking, and various flours, especially cassava and buckwheat, were added to the usual wheat flour in the manufacture of bread or even used alone in confectionery. Cassava, (arrowroot) and in the granulated form called tapioca, has never been incriminated, and Ordman, too, was unable to prove the case against this food. But buckwheat has been repeatedly found to be an offender, and in three bakers and confectioners asthma and coryza followed inhalation of buckwheat flour; in two symptoms also occurred after eating baked buckwheat products. Skin tests were strongly positive by the scratch method, confirmed by intradermal tests, but reactions were not as large as expected from the literature. Hyposensitization was attempted but results were doubtful.

FOODS AS A CAUSE OF ASTHMA

There has always been much discussion as to the proportionate role of foods in asthma. Foods can and do cause attacks, but usually dramatic episodes from certain foods are infrequent and are usually due to such foods as egg, nuts and fish. The great question is the possible hidden, less dramatic, role of foods in causing more or less chronic asthma and rhinitis. This question would not be necessary if we could rely on our skin tests, but it is usually only in the relatively few dramatic cases that food-skin tests are accurate, and coincide with the history. Opinions range from those of Rowe, Randolph and Rinkel who are strong food-allergy advocates to those of many allergists who believe that asthma and rhinitis from foods is rare.

Hill studied food sensitivity in 100 asthmatic children,[259] ages three to twelve. Thirty-five of these children gave positive scratch tests for one or more foods; in sixty-five the tests for foods were entirely negative. Hill did not try food-intradermal tests as he feels that this method is not reliable. (He states, however, that the intradermal tests for inhalant allergens are very valuable and usually are clinically important even when scratch inhalant tests are negative.) If these asthmatic children had remissions of three to four weeks, foods were not the cause of asthma, says Hill. But, if symptoms were continuous, foods were removed from the diet and reintroduced one at a time during asthma-free intervals (except with such dangerous and known causes as fish or nuts in particular cases.) Attacks had been or could be induced by specific foods in twenty-four cases, but in most of these the parents knew the offending foods and already avoided them. There were 218 positive scratch tests in the 100 children and forty-four of these tests (20 per cent) were clinically corroborated as causes of asthma. Egg white, fish, peanut, walnut, and chocolate comprised thirty-eight of these forty-four, with tomato a cause in two cases, and one each for spinach, orange, corn and barley. Despite positive tests for potato in twenty-two cases, Hill was never able to prove that potato caused asthma, and while spinach gave many positive tests, ingestion caused asthma in only one child. In sixteen cases (8 per cent) a food which gave a positive test caused irritation about the mouth, vomiting, urticaria, or angioneurotic edema, but not asthma (asparagus 1, banana 1, egg white 4, fish 2, orange 1, peanut 1, spinach 2, walnut 2). In 158 positive food tests ingestion did not cause symptoms; perhaps the child did not eat enough of that food.

Hill suggests that positive tests for foods may have the same significance as a positive tuberculin test, causing a positive reaction which may or may not have anything to do with the clinical condition, but may represent past sensitivity. Hill concludes that (1) 20 per cent of positive scratch tests for foods are etiologically significant in asthmatic children; (2) parents usually know which foods cause asthma and have already avoided them; (3) the most important foods are fish, egg, walnut, peanut and chocolate; (4) wheat and milk can cause asthma in children but are uncommon causes; and (5) food sensitivity is important in asthmatic children but less so than is sensitivity to inhalants. [Hill finds chocolate important; we rarely find this a factor in asthma, although important in migraine.]

Rowe and Rowe[429] disagree with Hill and others. In 411 children with asthma (up to twelve) foods were the sole cause in 50 per cent of the younger children (up to five), and along with inhalants responsible for another 38 per cent. In the older group (five to twelve) foods were the sole cause in 26 per cent, being associated with inhalant allergens in another 53 per cent. Inhalant allergy of all types was a major or secondary cause in 58 per cent of the younger group and in 71 per cent of the older. Foods were therefore more important factors in infancy but always remain important. Rowe and Rowe also attest to the unreliability of intracutaneous-food tests, and they feel that most people who have "colds and bronchial colds" which recur every two to eight weeks, especially from early fall to late spring, are really allergic, especially to foods. Respiratory infections are rarely responsible, and bacterial allergy rarely causes asthma. Of the inhalants pollens are much more important than animal emanations, house dust, fungi, or miscellaneous substances. They stress their standardized cereal-, egg-, milk-free diets as aids in the detection of food allergy.

In asthma in patients over fifty-five, Rowe and Rowe[430] again emphasize the importance of foods in etiology and their belief that bacterial allergy is of little importance. Food and inhalant factors were about equally responsible for the asthma in their patients. The recognition of the importance of foods depended chiefly on the routine use of their standard elimination diet. Clinical food allergy rarely could be demonstrated by skin tests. (The authors also discuss the management of those allergic to inhalants.)

Their report is based on 173 private patients over fifty-five who obtained good to excellent results from 1940 to 1946—none under treatment less than six months. The onset of asthma occurred after the age of fifty-five in fifty-one

patients, and between fifty and fifty-five in twenty-one more. The duration of asthma ranged from less than a year in twenty-two cases to over twenty years in thirty-eight. Asthma was perennial in 129, and recurrent exaggerations or attacks occurred in eighty. Other manifestations of allergy occurred, e.g., perennial nasal allergy in ninety-seven, and seasonal in thirty-three. There was a positive family history of asthma in eighty-one cases and of nasal allergy in eighteen.

As regards skin tests (they use the scratch technique with foods, scratch and intradermal with inhalants), Rowe and Rowe state that although skin tests were entirely negative in seventy-three of the 173 patients, fifty-eight were proved allergic only to foods, eleven to pollens and foods, and four to pollen alone—thus demonstrating the fallibility of skin tests in determining food allergy and, to a lesser extent, of inhalant allergy. In the 100 patients who gave positive skin tests grass pollen was positive in sixty-two, fall in fifty-three, tree in fifty, flowers in forty-five, animal emanations in forty, miscellaneous inhalants in forty, house dust in thirty-nine, fungi in eighteen, and foods in thirty-one.

[One can only comment that (a) these reports and that of Hill are at variance. Perhaps the routine use by Rowe of his elimination diets and the care with which his long experience has equipped him may well be the answer. No one believes that there is a great deal of difference in inhalant and bacterial environments between Oakland, California, and other parts of the country. (b) On the other hand, we are at a loss to explain the small number of reactions to house dust and fungi in Rowe's two papers. Perhaps if he used a potent dust extract, e.g. Endo's, his dust-positive cases would increase in number.] That care as regards foods is important is stressed by Rowe in his attention to details about the diet and his insistence that good results require (a) absolute adherence to the diet, (b) frequent conferences with the physician to detect willful or unintentional errors, and (c) realization that relief will appear in 2-14 days, depending on the time the allergens of formerly-eaten foods remain in the body and the time required for the lung cells to recover from allergic reactions. On his elimination diets sixty of the 173 patients gained weight, with no change in sixty-seven, desired loss of weight in twenty, and undesired loss, moderate in degree, in only ten.

Randolph[107] also has a long article on food allergy. Recognition of food allergy is obscured by several prevalent misconceptions. The facts are, he states, that (a) food sensitivity is as common in adults as in children; (b) patient's opinions of foods responsible are usually wrong when dealing with substances frequently ingested; (c) skin reactions to food extracts are unreliable and misleading guides for diet control; (d) any food may act as an allergen and expected incidence of allergic response is directly related to frequency of ingestion; and (e) inhalant sensitivity coexistent with food allergy should be treated before investigating the role of foods. Randolph discusses his method of food investigation which includes test meals with total leukocyte counts before and twenty, forty, and sixty minutes after the initial feeding. He has very clear tables and diagrams and he illustrates the cyclic aspects of food allergy. Corn is his chief offender, followed closely by wheat, milk, egg, potato, orange, beans, and other foods.

[From a study of such articles on food allergy as those just discussed and from our own experience with food tests done both by scratch and intradermal skin tests and also by clinical trials, we believe that foods are important causes of asthma as well as other allergic conditions. Inhalants are probably more important in the United States, but not in some other parts of the world. Everything which can cause or aggravate symptoms should be considered, including such predisposing factors as infection and emotions. Skin tests for foods should not be abandoned The scratch method for foods is fairly reliable, perhaps not as much as with inhalants. Intradermal food tests are less reliable but they should not be abandoned because they act as a check on the scratch tests and because we occasionally find a clinically important food allergen, e g. egg or cereal, by an intradermal test, though the scratch was negative Above all, let no one incline too much one way or the other.]

An Italian patient of Levy[100] developed severe asthma from eating fennel seed and sausage which contained fennel (closely related to the dill, carrot, celery, parsley and parsnip family). The seed is a favorite spice of Italians and is also used in medicines as an aromatic, stimulant and carminative. *Asthma was reproduced* by ingestion, and intradermal and passive transfer tests were strongly positive for fennel and fennel seed.

DRUGS AS CAUSES OF ASTHMA

Dragstedt[150] states that (a) drug allergy is indicated if resultant symptoms are those of allergy, e.g. urticaria, some types of dermatitis, angioneurotic edema

streptomycin but in her work was in contact with this preparation Passive transfer test was moderately positive. After forty-eight hours the site of the original intradermal test looked like that of a positive tuberculin reaction (Rosen[426]). Sonck[480] reports asthma in a woman physician who developed her symptoms not only by inhalation of salvarsan but also by absorption through breaks in her skin. Abdominal cramps, flushing of the face and urticaria also occurred, with some relief from antihistaminic drugs.

MISCELLANEOUS ETIOLOGIC FACTORS IN ASTHMA

Jose Cortez and his associates[132] tested sixteen dogs intracutaneously with common inhalants, foods and ascaris extracts, with positive reactions for extracts of house dust, feathers, goat and cattle hairs, orris root, ragweed, pyrethrum, tobacco, cottonseed, wheat, milk and soybean. Passive transfer was positive with dust, feathers and goat hair, but failed with pyrethrum. In two of these dogs the positive reactions were so clinically significant as to give further proof that allergy is not confined to man. In an effort to correlate the bacterial content of the air with allergy Frouchtman and his co-workers[204] identified eight different strains of bacteria (Barcelona). A most unusual happening occurred in Paris. A woman developed asthma and rhinitis from inhalation of horse serum with which she filled ampules. She gave negative skin and clinical tests for horse dander. Passive transfer was strongly positive with the serum, negative for dander. She was sensitive to raw horse meat, but not to cooked horse meat nor to any other animal serum (Blamoutier[73]).

A very important letter by Mills[131] states that "control of smoke production by the policing of the multitude of city flues has been demonstrated to be ineffective and is being abandoned in favor of regulations which make harmful smoke production impossible. Such regulations prohibit the sale of highly volatile coal for use in hand-fired furnaces and enforce a change to Diesel or electric power for railroad switching purposes within metropolitan limits as the two most important points in smoke control. In view of the exceedingly significant relationship of air pollution to respiratory disease death rates in industrial cities, it is important that those interested in personal and public health insist on really effective legislation whenever the matter is under consideration in their home community." This latter is all the more significant since the recent disaster in Donora, Pennsylvania, in which those who died or were seriously ill were, for the most part, victims of bronchial asthma or heart disease. [In our next review we should have authentic information on this disaster.]

Some predisposing factors are emphasized. Zivitz[570] stresses the importance of home environment, infections, irritating vapors, and meteorologic, climatic and psychosomatic factors. Based on a study of fifty allergic patients, eighteen of these could not be properly evaluated without attention to one or more of the above factors, and he points out that such a factor may explain the variable reactions to an antigen. Clusellas[118] studied attacks of asthma in each month of the year. He concludes that the meteorologic factor must be considered along with the psychogenic, allergic and reflex angles. Humidity, temperature, wind velocity and rain were not constantly involved in attacks of asthma but a rise in barometric pressure is asthmogenic; the patient is usually better when the pressure is low. The Weather Bureau officials were consulted but they did not believe that atmospheric changes were the determining factors per se; they said the relationship of allergens in the air as affected by barometric pressure may be important Jolicoeur[274] attempts to relate disturbances of the ovary to asthma.

Alvarinas and his co-workers[21] found that as many persons with allergy as without had intestinal parasites. In those with both allergy and parasites treatment of the parasites gave good and poor results. "Infestation with parasitic worms produces a hypersensitivity that is evidenced on skin test by an immediate wheal from intradermal injection of an extract and the finding of transferable antibodies (reagins). These facts provide the basis for the possibility that allergic manifestations such as asthma can be produced by hookworm infestation. Reports of authenticated cases were not found in the literature. Elimination of the hookworm infestation is the logical procedure in such a suspected case."[26]

Two papers question allergy as a cause of asthma. Jacquelin[270] says that only one-fifth of his cases are due to allergy; most are due to a constitutional disease, the treatment of which is the only way to get permanent results. This constitutional background is a mixture of disorders and dysfunctions of various glands and organs, the basis of which should be found in (a) heredity (neuro-arthritism and occasionally hereditary syphilis) and (b) tuberculous infection of early childhood. Hence treatment should include those usually given for allergy plus all

sorts of treatment of the exudative diatheses (cholagogues, sulphur, phosphoric acid, magnesium, et cetera, as well as measures for the supposed tuberculosis). Another paper by Lewi[301] states that hay fever is not due primarily to pollens [Blackley should rise from his grave] but is the result of abnormal conditions of the mucosa of the upper air passages. The author also believes that asthma is not due to allergens but to dysfunction of the sympathetic nervous system, and his treatment brings on hyperemia by the high frequency current applied along the spinal cord. Lewi claims complete and permanent relief in over 60 per cent of those treated (1,600 cases of asthma and related conditions), with great improvement in an additional 30 per cent.

[These last two papers should not go unchallenged. They are a throwback to our knowledge before clinical allergy became established. We used to talk glibly about this or that diathesis and we still know little about diatheses. Anyone who has been interested in asthma and hay fever knows that diatheses, except for the hereditary factor, mean little or nothing in these conditions. We do know that pollen causes asthma and hay fever and dust and other allergens lead to asthma and rhinitis in allergic persons, the local condition of the nasal mucosa being of little importance. The "marvelous results" obtained in the second paper cannot be accepted nor is the thesis of the first paper compatible with our present knowledge.]

The psychogenic factors in asthma will be discussed in the section on treatment (q.v.).

IMMUNOLOGY AND PATHOGENESIS

Easily the most outstanding paper of the year is by Warren and Dixon.[552] The location of the antigen-antibody reaction has been one of the most disputed aspects of anaphylactic shock. By using an antigen labeled with radioactive iodine and employing tracer techniques they have been able to recover sufficient antigen concentrations during the shock. The antigen was found in edematous bronchial fibrous tissue of the guinea pig. They then studied the stages in the development as well as the final picture of bronchial obstruction during shock and also bronchial obstruction produced by drugs acting on smooth muscle. Significant amounts of labeled antigen were found only in the liver and lung during anaphylactic shock. Since the amount of antigen taken up and its distribution in the liver were the same in sensitized and non-sensitized animals the liver evidently is not important as regards sensitivity. The startling finding was the fact that the affinity for antigen by sensitized lungs in fatal shock was about twice that seen in controls and therefore presumably a function of the sensitivity. The increased amount of antigen taken up by the sensitized lungs was found in edematous bronchial fibrous tissue. They were unable to confirm the generally accepted theory that bronchial obstruction of anaphylactic shock results solely from contraction of bronchial smooth muscle. Only in the early stages of shock (within two minutes after the onset of respiratory distress) was there convincing morphologic evidence of smooth muscle contraction, and even in these early stages there was already some edema. In the terminal stages of shock the smooth muscle did not appear contracted or otherwise abnormal. The bronchial edema which began to form during the early stages of shock became massive in the terminal stages and at that time appeared to be the most important factor in the production of bronchial obstruction. Since this edematous zone was the site of antigen localization, it seemed possible to the authors that the antigen-antibody reaction was related to the formation of edema.

[One cannot praise this work too highly. By the tracer technique with radioactive iodine they have given us authentic information. We have always believed that edema and excessive mucus formation were the important causes of the incomplete obstruction with resultant wheezing which is so characteristic of bronchial asthma. We have never thought that bronchospasm was important in asthma and there has been little or no verification of the theory of bronchospasm by bronchoscopists. Yet some writers persist in using the terms "bronchospasm" and "bronchial asthma" interchangeably. They are not the same, in our opinion, at least. When, at autopsy, one sees the extensive mechanical obstruction by the dried-out sputum he cannot but be impressed by the major role of edema and mucus. Hypertrophy of bronchial muscles does occur but only in chronic asthma of long standing. Heart failure is a rare cause of death in bronchial asthma. This paper goes a long way to substantiate the "edema" theory of asthma.]

To Miller[346] bronchial asthma is due to the pharmacologic action of histamine on the bronchi. This drug (a) dilates terminal arterioles and venules, (b) increases capillary permeability, causing swelling of the bronchial mucosa, (c) stimulates smooth muscle, causing bronchospasm, (d) stimulates exocrine glands, causing an

outpouring of mucus from bronchial glands, (e) stimulates sensory nerve endings, causing itching and cough, and (f) calls forth eosinophiles. The three factors which lead to narrowing of the bronchi (spasm, mucus and edema) in turn cause emphysema, hypoxemia and hypoxia. Anything which can cause the above phenomenon can cause wheezing and dyspnea, e.g. a foreign body or pressure from without by a tumor or aneurism—in other words, bronchial asthma is not necessarily an allergic phenomenon. [We strenuously object to this latter statement. We believe that true bronchial asthma is always allergic. It is true that in perhaps 20 to 25 per cent of the cases we fail to find the causative factors. Nevertheless, if we search and continue to search we will, in many patients, ultimately find the cause, with benefit to the patient. We believe that non-allergic conditions, e.g. foreign bodies and tumors, should not be listed as causes of bronchial asthma even if they do cause "asthmatoid" symptoms. They constitute the diseases which we will shortly discuss in the section on differential diagnosis. Furthermore, we by no means agree with Miller's wholehearted acceptance of the histamine theory as the cause of the symptoms of bronchial asthma and other allergic diseases.]

Abramson,[3] among others, stoutly denies the histaminic theory of allergy, and quotes seventeen experimental findings which are incompatible with that theory, among them the fact that antihistamine drugs can control bronchial obstruction due to histamine but not when due to allergens, whereas epinephrine readily controls both.

Bronfenbrenner[83] believes in the "unitarian" hypothesis of hypersensitivity and immunity: the phenomena of specific heightened resistance and heightened sensitivity are different expressions of a single biologic process. Only one antibody is produced and this can be recognized by a variety of procedures, some direct, others indirect. Burnet,[97] also an immunologist, believes that genetics and immunology will soon be linked in a productive attack on some of the most fundamental problems of biology. From such an attack may come knowledge of high significance for human medicine, not least in the field of allergy. Cooke[126] points out that in spontaneous (hereditary) asthma and rhinitis the vasodilation, with edema in sensitized tissues, and the increased secretion of mucus all occur promptly on exposure to an allergen, e.g. a cat. H. Miller[314] has diagrammatic sketches in his article on the immunologic basis of clinical allergy. He also has a nice table differentiating the characteristics of normal antibodies and reagins.

PHYSIOLOGY OF RESPIRATION AS RELATED TO ASTHMA

An editorial in the ANNALS OF ALLERGY[170] emphasizes the importance of the physiology of the lungs in asthma. It quotes a recent paper by Mack, Grossman and Katz[325] which shows that pulmonary congestion may cause dyspnea. Mechanically, changes in the distensibility of the lungs are important. When pulmonary vessels become engorged they are more rigid and act like a hose turgid with water under pressure. It is readily accepted that this engorgement contributes to the increased respiratory effort observed in congestive heart failure. But this diminished distensibility may also diminish vital capacity and even cause intrapleural exudation. By injecting blood into the pulmonary circulation of dogs the distensibility of the lungs is proportionately decreased. When almost all the injected blood was siphoned off the distensibility curve was restored. This demonstrated clearly that the effect was due to intravascular blood which could be siphoned off and not to an intra-alveolar transudate similar to that found in pulmonary edema. In the living animal two or three of the pulmonary veins were clamped at the entrance to the left atrium. This acted much like a severe mitral stenosis with pulmonary congestion. The volume-pressure curves obtained then showed decreased distensibility of the lungs.

Brown has an excellent review of the physiology of respiration especially as it affects bronchial asthma.[86] He concludes that "respiration is a complex biological mechanism, stimulated, depressed and affected by many varied and diverse factors, no one of which operates alone." He agrees with Gray that "while a number of factors exert independent effects upon respiratory ventilation, they are also mutually interdependent, so that a change in any one factor usually brings about changes in one or more of the other factors, the actual ventilation being defined as the algebraic sum of the partial effects of the separate agents. Since these lend themselves to mathematical description, it is possible to reduce them to working formulae."

Hickam and Cargill[257] *took* advantage of the newly popularized technique of intracardiac catheterization with penetration into the pulmonary artery. With eight normal individuals as controls, they tested many patients with cardiovascular disease

in the vascular filling of the lung is produced, the breathing lung dilates, producing a true emphysema and at the same time a rigidity which makes expiration difficult. Thus, on increasing resistance in the pulmonary veins, the same phenomena are noted as in experimental asthmatic shock. The authors believe that both bronchial and cardiac asthma are sequelae of acute ingurgitation of the smaller circle. Drugs which cut short asthmatic crisis act by diminishing the volume of pulmonary blood.

Colldahl[125] states that in most severe attacks of asthma the ventilation of the lungs as well as the intake of oxygen is much lower than between attacks. When the attack is over the intake of oxygen is considerably raised. In mild asthma the pulmonary ventilation and oxygen intake are much higher than normal. [This does not apply to forced rapid breathing tests, as previously mentioned.] The intake of oxygen during such an attack may be increased at least 100 per cent. The systolic and diastolic blood pressures are usually considerably increased during severe spells, along with a fall in body temperature. There is often a moderate rise in temperature in mild but persistent asthma.

In 100 patients with asthma, Hamburger[236] measured the "average expiratory rate" (A.E.R.), i.e., the maximal quantity of air which can be expired in one second. He found that in 85 per cent of the cases, with no apparent dyspnea, the A.E.R. was 20 to 50 per cent lower than normal. In 11 per cent, with permanent dyspnea between attacks, the A.E.R. was more than 50 per cent below normal. This proves that in many asthmatic patients who appear to be symptom-free between spells there is a permanent subclinical respiratory deficiency. [Of course, one could guess this by questioning asthmatic patients closely as to how much exertion they actually can tolerate when they say they are free from asthma. Probably the only ones who are 100 per cent symptom-free between attacks are those more fortunate individuals who are allergic to substances which they only meet at long intervals, e.g. a certain pollen or animal or a food eaten only occasionally, e.g. a particular nut. The A.E.R. is, however, useful, although the ventilatory capacity test or the B.R. test, just described, are much more accurate.]

PATHOLOGY OF ASTHMA

Deaths continue to occur even though the incidence is very small as compared with the number of attacks. The findings at the autopsies recently reported are much the same as in previous years. A thirty-four-year-old asthmatic patient of Wakefield and Hirsch[510] entered the hospital for the fourth time but she failed to respond to the usual measures. Coma set in with death on the third hospital day. At autopsy the usual inspissated mucinous obstruction of the bronchioles was found, along with emphysema. The left lower lobe also showed atelectasis, hyperemia and bronchopneumonia; focal atelectasis in the lower right lobe and focal fibrinous pleuritis at the right apex. Death apparently came from suffocation. [Bronchoscopic aspiration was not done—it might have prolonged the patient's life; we have undoubtedly saved several lives by enlisting the services of a bronchoscopist when the usual therapy proved unsuccessful. We strongly recommend bronchoscopic aspiration and without too much delay.]

A three-year-old asthmatic child of Tichenos and Lafsky[510] died fifteen hours after admission to the hospital. Again death was due to generalized bronchial obstruction from excessive mucus plus pulmonary emphysema. In addition, right heart failure was diagnosed, and a throat culture was positive for hemolytic staphylococcus aureus; a culture of the lungs and bronchi revealed Gram-positive diplococci resembling pneumococci. The whole picture was that of overwhelming infection in an asthmatic child. [In reviewing this case Glaser (and we agree) said that in such an emergency as this more 1:1000 epinephrine should have been given, along with aminophyllin by vein, dextrose, sulfadiazine, penicillin and oxygen. In such a case one should push large doses of penicillin without waiting for culture report.]

In Andre's case,[22] a sixteen-year-old girl died suddenly in the third attack of asthma which had occurred in the space of twelve days. The most characteristic sign was Kussmaul's pulse: weakening or disappearance of the pulse during inspiration. The mechanism of this paradoxical pulse is discussed. A sixty-four-year-old male asthmatic patient died during an attack fifteen months after the onset of asthma. Alexander, Wilson and associates[17] could find no personal or family history of allergy nor any eosinophilia nor Curschmann's spirals. Nevertheless, at autopsy there were the usual findings of fatal asthma: mucous plugs in all the secondary and terminal bronchi; generalized emphysema, hyalinization of basement membranes; hypertrophy of the muscular coats and infiltration with eosino-

philes. In addition, calcified nodules and lymph nodes were noted, along with moderate dilatation and hypertrophy of the right ventricle.

From France, where morphine is rarely used in the treatment of asthma, Villanova[537] says death from asthma seems to be increasing in frequency. Death, he believes, is due either to (a) a sudden unexplained cause, (b) anaphylactic shock, (c) heart failure or (d) asphyxia due to bronchial obstruction. He adds three more fatalities, all adults, all of whom had received great quantities of varying medications. He especially blames the sympathomimetic drugs (frequent factors), morphine (occasionally), and novocaine (some cases). He advises venesection, intravenous aminophyllin, with or without novocaine, phenobarbital subcutaneously, and injections of pilocarpine. [Sclafer, in commenting, also believes that an excess of epinephrine is a frequent cause of death. Less than 10 per cent of French pediatricians dare to use this drug in asthmatic children.]

Jiménez-Díaz and Lopez-Garcia[273] also report a fatal case of asthma. "Bronchial spasm" is a poor term because at post-mortem there is no basis for this diagnosis. Status asthmaticus, as already mentioned above, is due to obstruction of the whole bronchial tree from secretion plus hypertension of the lesser circulation which in turn causes rigidity of the lung which in turn causes difficulty in expulsion of secretions from the lungs; this in turn thickens the secretion, with an increase in obstruction.

In a fifty-one-year-old man who had asthma for about seven years the usual measures plus bronchoscopic aspirations (no morphine) failed. Melich and his associates[337] report that autopsy led to the final diagnosis of intrinsic bronchial asthma, bronchopneumonia and mild cor pulmonale. Mucous plugs were very numerous, with generalized emphysema. The right ventricle appeared slightly enlarged. In Galup's case[212] death occurred after only eight years of asthma in a man who had asthma, emphysema, chronic bronchitis, nasopharyngitis and recurrent acute pneumonitis. A unique feature in this case was the fact that the patient's diaphragm was normal in 1942, flattened bilaterally in 1943, and paradoxical in 1945, moving upward with inspiration. The cause of the phrenic paralysis was discussed but there was no definite conclusion.

In Gay's article on the Pathology of Asthma[216] he reviews the literature and adds twenty-four cases from Johns Hopkins Hospital with a clinical diagnosis of bronchial asthma either as a primary or secondary cause of death. [These cases were also discussed in his book mentioned in our last review.[521] Deaths can often be prevented by the prompt use of penicillin in any acute case in which infection is present or suspected; three of the twenty-four deaths were in children, in whom infection is frequently severe and sudden.]

In Peterson's case[383] death followed mediastinal and subcutaneous emphysema which occurred during an attack of asthma. Up to 1945, twenty-six cases of spontaneous emphysema of this type had been reported in asthma, with no fatalities. In this case death occurred in a twenty-year-old primipara, gravid four months, who entered the hospital with severe dyspnea and anxiety. She had asthma for eight years but none for the two years preceding this pregnancy. Asthma returned in the second month of pregnancy and became progressively worse. Extreme restlessness was not controlled by oxygen, helium, aminophyllin, barbiturates, ether in oil, and even demerol and a little morphine. On the second day swelling of the neck was noted, with spread to the face and anterior thorax and increased respiratory distress and death thirty-six hours after admission. At autopsy plugging of practically every small visible bronchus was found. The mediastinal and subcutaneous tissues of the neck, face and thorax revealed marked emphysema, but no pleural air was found when the lungs were opened under water. The outstanding findings were the large amounts of mucus with plugging, widening and hyalinization of basement membranes and numerous eosinophiles. The muscles of many large bronchi were hypertrophied but that of many smaller bronchi were thinned with small areas of saccular bronchiectasis. The author states that since all the other cases recovered the cause of death in this case was undoubtedly bronchial asthma; the use of morphine was a serious error. The associated subcutaneous emphysema was, in all likelihood, not responsible for the exitus. Even the use of demerol in asthma is of doubtful value. [We agree, and recently, in addition to our absolute avoidance of morphine in bronchial asthma, we are using less and less demerol; the less sedation the better the results.]

A twenty-year-old sailor, known to be egg-sensitive, died twenty-six minutes after an injection of typhus vaccine. Autopsy revealed only intense pulmonary congestion, according to Walker.[547]

Two other papers on pathology should be mentioned. Bohrod, whose lectures and slides on asthma and related conditions are superb—they should be put out

in book form—classifies the histologic reactions in allergic diseases.[76] Anatomic differences in these lesions divide them into a relatively small number of groups each of which also has clinical and immunologic similarities. No lesion is pathognomonic of allergy but all are highly characteristic and their presence suggests allergy as a cause. But many of the lesions can be both allergic and non-allergic in origin. Bohrod classifies the diseases of allergic and possible allergic origin, according to their histologic lesions (necrotizing, cell selective, anaphylactoid, and granulomatous). Asthma, anaphylaxis, serum sickness, atopic dermatitis, caseous tuberculous pneumonia, and rheumatoid pneumonia belong in the anaphylactoid group.

According to Soulas[482] deficiency in the defense power of the bronchus is due to (a) changes in the bronchial wall with edema with possible resultant erosive inflammation or ulceration and sometimes associated with an involvement far below the surface, e.g. necrosis, stenosis or new growth; whether superficial or deep, the parietal lesion lessens the secretion of mucus. (b) There is also deficient expulsion of bronchial secretion, due not only to the deficient vector represented by the cilia and the mucus, but also to (c) lessened motility of the wall. As a result, obstruction, stagnation and retention may occur. Bronchoscopic treatment should try to relieve obstruction by clearing the bronchi and by restoring their secretory, excretory and motor power.

SYMPTOMATOLOGY OF ASTHMA

Since the symptoms of asthma have been adequately described, even many years ago, most papers in this field deal with classifications, laboratory aids, and complications. Many are concerned with asthma in children, with a few about the elderly.

Simon[471] discusses the definition and language of allergy, its origin, development and significance, and allergenic interrelationships. Is histamine actually the substance, or the only substance, involved in allergic reactions? He discusses various aspects of the pathogenesis of asthma, with no definite answer.

To Rackemann[402,405,406] asthma is both a symptom and a disease. The typical patient can wheeze from a great variety of causes of which allergy is only one. Patients who develop asthma before thirty are "extrinsic" in type, although there may be complications, e.g. infection or "depletion." If asthma begins after forty they are "intrinsic" and associated with bacterial allergy, "depletion," psychosomatic factors, and occasionally with tumor or foreign bodies. [As pointed out in previous reviews, this classification by age into "intrinsic" and "extrinsic" seems to us to be a block in the road toward solution of the problem. When one says "intrinsic" he is apt to give up, to tell the patient to go to Arizona or California or Florida or into the mountains or down to the coast. We feel that there is little distinction between the two groups—both have about equal eosinophilia in the blood and sputa, and both have similar wheezing, dyspnea and cough. In the "intrinsic" group the patients are older and there is naturally a greater tendency to cardiovascular complications, to chronicity, to loss of morale and weight, and because the skin of older people is less sensitive, to more negative skin tests. But we have found positive skin tests in many elderly asthmatic patients and have occasionally had negative skin tests in children with asthma. Very recently, we relieved the symptoms in two men by finding positive test for karaya gum, used to hold up their upper dentures. Many allergists never test for karaya gum; they would have called these two patients intrinsic because they were elderly and because other skin tests were practically negative. And experienced clinicians like Rowe have shown, as previously stated, that many older asthmatic patients are allergic to foods in spite of negative food-skin tests.]

To Baagbe[42] "allergy" means "a changed sensitivity due to the formation of antibodies." Thus his "allergy" includes both anaphylaxis and immunity; the definition is on a serologic basis. He considers three factors: (a) a main disposition to become allergic, (b) an accessory disposition toward a particular allergic condition, and (c) in rarer cases an inherited allergy to a particular allergen, e.g. egg.

Farrerons-Co[176] reviews other classifications of asthma, then submits his own:

(a) Endogenous (mild, moderate, severe)
(b) Infectious (focal, bronchial)
(c) Parallergic (due to pure parallergens or bacterial parallergens)
(d) Allergic (foods, inhalants, mixed foods and inhalants)
(e) Combined (allergens and bacteria) (bronchitis)

Alemany-Vall[524] discusses lesser allergies, either manifest or hidden, e.g. sinusitis, tracheobronchitis or mild asthma, as well as various types of allergy in other parts of the body. Forman[190] mentions certain clinical aspects of asthma, and Baagbe[43] rightly emphasizes the importance of pre-asthmatic bronchitis, with severe attacks of cough without wheezing, or winter attacks of bronchitis over many years in children, often associated with fever and frequent "colds"—all these symptoms finally, though not necessarily, culminating in a real attack of asthma.

Philps[384] describes a thirty-year-old patient who has asthma, eczema and cataracts. The latter two are associated fairly frequently, but the additional presence of asthma is very rare. Since the lens is ectodermal in origin it is not surprising that it should develop defects when the skin and epithelial lining of the air passages are also affected. Her asthma was so severe that the cataract operation had to be performed with the patient sitting up. Peralta and Valle[380] emphasize history-taking in bronchial asthma, and Bruce-Peterson[92] was surprised to learn that in the United States 50 per cent of patients with hay fever develop asthma unless properly treated. In Britain there is no ragweed and therefore the incidence of pollen asthma must be much lower.

In a two-year-old patient of A. Brown,[84] attacks of asthma followed periods of intense craving for and indulgence in carbohydrates. With each spell of wheezing and dypsnea the stools became loose, frothy and offensive; then the craving for sweets disappeared, the stools returned to normal, and the attacks subsided. A high carbohydrate diet brought on symptoms within twenty-four hours. Irritability was a striking symptom, but all symptoms again subsided when a low carbohydrate diet was substituted for the high. [Despite the diagnosis of asthma in this case there appear to be no diagnostic features of allergy, e.g. family or personal history, positive skin tests, or eosinophilia. We wonder if hypoglycemia of some type might be a factor perhaps due to an adenoma of the pancreas; for occasionally, in diseases involving the middle layer of the cortex of the adrenal glands, a heavy carbohydrate meal is followed by prolonged periods of hypoglycemia. Blood sugar and other tests should be carried out.]

Another interesting case occurred in a seventeen-year-old asthmatic boy. Digestive symptoms were also marked for about a month, and when x-rays revealed a huge stomach 0.03 gram of ephedrine was given daily, later three days a week, for a total dose of twelve grams over a period of sixteen months. The symptoms were alleviated and the stomach shrunk to normal size (Hillemand and associates[260]). This case is analogous to that of Zeller's patient, a sufferer from asthma and hay fever, whose asthma was relieved by an intravenous injection of 0.50 gm. aminophyllin. In addition, her marked abdominal distention (intestinal obstruction?) also disappeared. Several other episodes of distention in Zeller's patient were also promptly relieved by aminophyllin.[566]

Conn and Wolf[124] found that those with allergic respiratory tract disease, chiefly asthma, had increased palmar sweating as determined by the Silverman technique, and as compared to other patients with psychoneurosis and others with syphilis. Race, sex, and age were without influence. The increased perspiration is thought due to disturbed water balance and to cholinergic stimulation. They conclude that allergic respiratory disease in man is dependent on an inherent behavior pattern of the autonomic nervous system in addition to hypersensitivity.

Feinberg[177] discusses allergic problems of the railway surgeon. These consist of (a) allergy in employes, not related to the unemployment, (b) allergy due to conditions of employment, and (c) allergy relating to passengers and the public. Railroads are advised to (a) lessen the amount of smoke, (b) have available dust-proof casings for mattresses and pillows of allergic passengers, and modifications of diets which could be substituted for such foods as egg, wheat and milk, and (c) have ready information for passengers concerning pollen and fungus counts in various parts of the country.

ASTHMA IN CHILDREN, WITH REMARKS ON TREATMENT

This subject has provoked many articles. Dees and Lowenbach[149] found cerebral dysrhythmia, chiefly occipital, in fifty-two of eighty-five allergic children, with no relation to behavior problems in these children nor to convulsive history or findings. The incidence was higher among children with persistent allergic symptoms. The percentage of this dysrhythmia was about 50 per cent nonallergic children, even in those with convulsive disorders of behavior problems.

Nance[356] reports seven cases of asthma in the newborn—it is probably the most frequent cause of wheezing in infants. One should not accept the diagnosis of thymus enlargement as the cause of noisy respiration in the newborn on the basis of roentgen observations alone. At this age the cause is almost always dietary

and detection and removal of the offending food is simple. Hill[258] says that atelectasis can occur in the newborn, usually due to aspiration of amniotic fluid. Bronchoscopy should be done as soon as possible. And Cohen and Abram[123] utilized the grid technique described by Wetzel to study growth patterns. From 503 observations in 150 allergic children seen in private practice as compared with 622 observations on 102 nonallergic controls, they conclude that (a) allergy occurs more frequently in children (especially boys) who, by inheritance, are constitutionally slender; (b) allergy is a common cause of growth failure; (c) control of active allergy is accompanied by a corresponding growth repair if an adequate diet is available.

Black[69] states that the incidence of childhood infections in asthmatic children is no greater than in those who are non-asthmatic. He has never seen pulmonary tuberculosis in an asthmatic child under the age of ten, and death from asthma in children is very rare. Julia Baker,[45] in a seven-year study, believes that altitude is important in initiation and severity of allergic reactions. Symptoms are unduly common and severe at the high altitude of Mexico City (7,325 feet) and appear frequently in children not noticeably affected at lower altitudes. In 1000 children 509 were allergic, and sixty-two were sicker in Mexico City than when they lived at lower altitudes. Symptoms frequently followed ingestion of such foods as egg, milk, orange, chocolate and wheat. Infection was not a factor as shown by studies of blood and stools. Mexican children and those from the United States and other countries were about equally affected.

Glaser,[223] in his annual review of pediatric allergy, has an excellent summary of psychosomatic aspects. The child's symptoms should not be discussed in front of the child but it should be told that it is progressing nicely and encouraged to play as much as possible. However, the best that can be hoped for from the psychologic approach is amelioration, rarely a cure, because no psychological treatment can change the underlying allergic constitution. Once we are able to relieve, at will, the allergic manifestations, the psychological problems associated will, in most instances, solve themselves." Glaser stresses the seriousness of asthma in infants and children. Prompt therapy is necessary and should include epinephrine, aminophyllin, oxygen, bronchoscopy, penicillin, and/or sulfa drugs.

There are several more general papers. Bowen[78] has a fine article on asthmatic children. He stresses a good history. In one group 90 per cent had a positive hereditary factor, and when inheritance was bilateral 90 per cent of the children developed allergic symptoms before ten; with unilateral inheritance about 30 per cent. Those who are milk-sensitive are given dicalcium phosphate and Mullsoy, Allerteen or goat's milk. He believes, with Ratner, that those who are allergic to corn can safely eat foods with pure corn syrup, Dextrimaltose and crystalline sugars. Food skin tests are less than 40 per cent reliable. Some foods can be tolerated once a week but not three or four days in succession. Food dislikes are not necessarily associated with allergy; a child may like an allergenic food. The fewer the nose drops the better—when necessary he prefers Neosynephrine ¼ to ½ per cent. He has an excellent outline for treatment, with remarks on the use of epinephrine, study of the home, hobbies (e.g. glue exposures), and complete avoidance of morphine. And, like Glaser, his allergic children are encouraged to play as much as possible.

Logan[313] uses scratch tests in children up to five, with a few selected intradermals. Older children receive intradermal tests except for foods—he uses only thirty-six antigens for routine testing. He points out that asthma in children is often incorrectly diagnosed; the child may merely have excessive saliva or mucus, or an acute laryngotracheobronchitis, or even "sighing dyspnea," among other conditions. [We do complete scratch testing (about 200 or more) in all allergic patients, from infancy to old age, and follow by intradermal tests when sufficient information is not obtained. In infants the chest and abdomen are usually used, in older children and adults the arms. One is often surprised to find a positive reactor which fits in clinically even though a painstaking history was negative for this allergen—witness those who are allergic to cottonseed or karaya gum.]

In 265 children with asthma, Buffum[96] found eighty-five (32 per cent) with onset before the age of two. Of these, twenty-nine (34 per cent) were severe as compared with thirty-seven (20 per cent) with onset after two. Superimposed infections frequently increase and prolong the bronchial reaction, with excellent results from sulfadiazine and/or penicillin. Skin tests in children were invaluable, and 61 per cent of his children were completely or almost completely relieved of their symptoms, with 87 per cent helped (three-year followup).

Archibald[40] stresses the long-range point of view in allergic children. He uses scratch tests on the back, with positive reactions in about 75 per cent of cases of re-

spiratory allergy. He likes the Rowe-type diets and emphasizes avoidance of house dust. McGee[321] studied 150 healthy babies to recognize allergic tendencies at their onset. Foods were given one at a time and the babies seen once a month. Persistent food dislikes did not parallel food allergies. Foods which caused symptoms during the first year of life, in order of frequency, were orange, boiled cow's milk, spinach, ascorbic acid, mixed cereals, prunes, tomato, codliver oil, carrot, oat, and wheat. McGee[322] also points out that "croupy" infants frequently develop bronchial asthma or bronchitis. If tonsils and adenoids are removed outside of the pollen season hay fever and asthma occur less frequently. Epinephrine is excellent for respiratory symptoms, especially in unilateral atelectasis. [We in the United States frequently use small doses of epinephrine in asthmatic children. Those in France, Cuba, and perhaps other countries seem afraid of this drug. Could they be injecting epinephrine stronger than our standard 1:1000 dilution?] McGee says that when skin tests are necessary for children under seven or eight the passive transfer method is best. It prevents needle-phobia [what about ordinary immunizations?] and does not destroy the child's morale. In addition, an adequate survey is possible in any place since the defibrinated sterile plasma, and the summary of the history and physical findings can be sent by mail to the allergist. [This revolutionary technique smacks of "mail-order" medicine. We certainly strongly oppose such practice as there is no substitute for a personal history and examination of patients. Furthermore, skin tests can easily be made in children of all ages, especially if the scratch technique is used to begin with. All one needs is a little patience and a kindly and playful attitude with these children; the removal of a parent may help.]

In Honolulu, Myers[351] says molds are more important than pollen. He also discusses differential diagnosis of asthma in children. He uses intradermal tests but says he "guards" against possible danger by having epinephrine and a tourniquet on hand, and just omits testing for those allergens which give a positive history. He only makes six to ten tests at a sitting. If all skin tests are negative he uses Hapamine. O'Keefe[364] says foods are the most common cause of asthma in children under three; from three to seven animal emanations are most important, and after seven, pollens lead, with bacteria later. He uses scratch tests, supplemented by intradermal tests if necessary.

Pounders[393] says that treatment should be as simple as possible so that it can be carried out. He quotes Shakespeare: "If to do were as easy as to know what were good to do, chapels had been churches, and poor men's cottages princes' palaces." General papers on allergy in children also come from Bentolila,[58] Pennington,[377] Slesinger,[474] and Smyth, Bowen, et al.[479] Rucks[433] emphasizes the difficulty in differentiating the infectious and allergic types of asthmatic bronchitis in children, especially if the allergic condition is associated with some other type of chest disease.

Prophylaxis in children is discussed by Shulman,[468] especially as regards new foods and the environment. Roberts[420] wrote "Protecting Your Child from Allergy" in *Hygiea* magazine. The article is very good, although Glaser rightly says "Roberts, a layman, quotes various pediatric allergists as having made the statement in a round table discussion at the ninth annual meeting of the American Academy of Pediatrics to the effect that 'Fifty per cent of the allergic cases in the nation may be avoided by stressing certain preventive measures which parents can take.'" Glaser adds "it is unfortunate that such a dogmatic statement should have been made in a journal intended to inform laymen on the progress of medicine, since there is no scientific evidence whatsoever of the truth of this statement. There is at present only presumptive evidence that allergy may be prevented by use of certain measures which are very reasonable and should be carried out because of this and the equally important fact that they can do no harm."

From Sweden, Salen[438] discusses the diagnosis, treatment and prognosis of asthma in children. Of eighty-five children with severe asthma, recovery, complete or almost complete, occurred in seventy-four (94 per cent). His therapy is similar to ours except that his patients also inhale eucalyptus tar. The prognosis is good if treatment is begun before the onset of such complications as emphysema or purulent bronchitis.

Horesh[263] has two interesting case reports. An eight-year-old girl developed convulsions four hours after the eighth injection of ragweed extract. It was felt that the convulsions had nothing to do with this injection but when an increased ragweed dosage was given a week later even more severe convulsions occurred in four hours. Hyposensitization was stopped with no further convulsions in the following five-year period. The author agrees that the second injection should not have been given. [Bizarre reactions occasionally occur during hyposensitization. We have a ragweed-hay-fever-asthma patient in whom small dosages twice brought

on unexpected vaginal bleeding. Much smaller dosages have been given without further trouble.] Horesh's second case is "sighing dyspnea" in a thirteen-year-old girl whose brother has asthma. The mother was certain the girl was also developing asthma, and the girl had an almost uncontrollable desire to fill her lungs with air at five or ten minute intervals, taking deep breaths and complaining that she had difficulty in taking them.

In Bowman's series,[79] 90 per cent of twenty-five cases of purely infectious sinusitis, without allergy, were cured by x-ray therapy; this treatment was followed by clearance of sinuses, disappearance of thickened membranes, and lessening of lymphoid hyperplasia in the nasopharynx. In many of these cases the child's cough is the predominant symptom, and the sinusitis which causes the cough is overlooked. The ethmoid and maxillary sinuses are most commonly infected in children. In addition to x-ray treatment it may also be necessary to use nasal vasoconstrictors judiciously, to eliminate allergic factors, if present, to remove infected tonsils and adenoids, and to correct any nasal abnormalities which block drainage.

DIAGNOSIS OF BRONCHIAL ASTHMA

In a scientific exhibit in June, 1947 (American Medical Association), and later published,[522] L. Unger, H. Levy, A. H. Unger and Eisele outline the diagnosis, complications, differential diagnosis, causes, and treatment of bronchial asthma. Included are four murals depicting "Asthma Through the Ages," as well as x-ray films, photographs of twenty men whose contributions have been outstanding in this field, and pathological studies.

Samter[440] found Charcot-Leyden crystals in the blood of patients with high absolute eosinophilia; the crystals originate in individual eosinophiles, but crystals develop in only a minority of eosinophiles. Dutton[166] studied forty-three patients of whom thirteen were allergic, ten infectious, and seventeen allergic-infectious, with asthma in twenty-six cases. He found that "the Weltman reaction is somewhat more efficient than the sedimentation rate as a diagnostic aid. This is particularly true in borderline cases (as to presence of allergy and/or infection). We believe that these two tests, the Weltman reaction particularly, are valuable aids when determining those patients who have either a primary or complicating infection." Frouchtman,[202] in a study of the sedimentation rates in 160 allergic patients, found the rate slow in seventy-six, normal in seventy-two and fast in twelve. In patients with focal infection slow rates have been found, thus demonstrating that when the focus is allergenic rather than septic the rate is not quickened. Livington[304] has shown that asthmatic children with high sedimentation rates may be greatly benefited by irradiation of nasopharyngeal tissue. All but one of twenty-two asthmatic children successfully treated by radon had elevated rates, whereas of eleven other children who were not helped by this therapy only one had a slightly increased rate. In the successful cases lymphoid tissue entirely disappeared from the nasopharynx and asthmatic attacks vanished, recurred occasionally in mild form, or were less than half as often or as severe as before treatment. These children were under observation for six months to four years, and elevated sedimentation rates returned to normal in all but one of the successful cases.

Wiswell and Rackemann[560] have a long article on chemical factors in asthma, with an extensive review of the literature. They found that: (a) acid-base balance: potential alkalosis is not a constant factor. The poor pulmonary ventilation causes a retention of excess carbon dioxide in the blood with a compensatory rise in plasma bicarbonate level and the administration of hydrochloric acid to such patients increases the excess of carbon dioxide. If this excess cannot be eliminated through the lungs there may be an increase of dyspnea. Administration of alkali only temporarily compensates for excessive carbon dioxide. (b) The sodium potassium and water balance data are confusing. There is no indication that changes in these are specific or fundamental in asthma. Any marked shift in water balance may aggravate or improve asthma. (c) Calcium, phosphorus and magnesium are unimportant in asthma. Any beneficial effects from treatment with these probably results from action on the neuromuscular mechanism. (d) The blood sugar has no relationship. (e) The role of cholesterol and fat metabolism in asthma is not clear. (f) Although deficiencies of vitamin C or niacin probably do not cause asthma they may aggravate existing asthma.

Finlayson[186] has a comprehensive paper on laboratory guides in asthma, especially as regards the importance of eosinophilia in the blood and sputum. Delafontaine and Pistre[150] report that attacks of asthma were accompanied by blood retention of nitrogen in a sixty-five-year-old female observed over many years. In twenty asthmatic patients Serafini and Lauricella[458] determined the potassium

blood level one, two, three and four hours after ingestion of four grams of potassium chloride—the level in asthmatics was 28.5 per cent higher than in normals; levels returned to normal in asthmatics in four hours or more, in two to four hours in normal persons. The presence or absence of an attack did not change results. Serafini and Brozzo[462] also injected 2 c.c. 2 per cent Antergan intravenously; the potassium levels in six asthmatics increased almost threefold as compared with that in six normals, with the highest levels fifteen to thirty minutes after injections. The calcium levels were slightly depressed. Serafini and associates[463] induced fever in asthmatic patients and found a decrease in the alkaline reserve and a decrease in lymphocytes, eosinophiles, and potassium during the fever. Since they found that the fever treatment gave relief they believe that the fever changes symptoms from vagotonic to sympathomimetic. Low blood sugar levels were the most consistent finding in ninety-two patients with intrinsic asthma, say Christensen and Seidel[112]—patients with marked debility, weakness and weight loss. Asthmatic patients may have some hyperinsulinism.

Skin tests are discussed in five papers. Christensen and Sonne[113] believe we rely too much on skin tests, especially with food extracts. One child who was forbidden eggs because of a strong skin reaction subsequently ate three eggs each morning without symptoms. [In our experience such an occurrence has never occurred. We repeat all positive scratch tests if the patients say they are not troubled by the particular food. Almost invariably the repeated test will be negative if the patient is clinically negative; dermographia must, of course, be ruled out.] Pepys[379] also discusses the various types of skin tests, including those by electrophoresis. Tests with foods are not nearly as reliable as with inhalants.

Taub[505] has practically abandoned the scratch test because it is so much less sensitive than the intradermal. He admits that utmost caution must be exercised with the intradermal tests in those sensitive to such potent allergens as cottonseed, linseed, kapok and fish. If the history indicates one of these he advises preliminary scratch tests. [The fallacy of this procedure lies in the fact that, to our knowledge, no cottonseed-sensitive patient has ever suspected this sensitivity until informed by the skin test. Not even an allergist has enough time to ask about possible sensitivity to each and every extract he uses. Why take chances? Too many deaths have followed intradermal testing. The only possible excuses for limiting tests to the intradermal method are sheer unwillingness to do a large number of preliminary scratch tests or a stubborn idea that scratch tests are not worth while. We wish all doubting Thomases would try for themselves the scratch technique with such allergens as egg, fish, nuts, Endo house dust, pollens, fungi, and animal emanations, to mention the most important. We frequently obtain four to six plus scratch reactions to these—and we certainly would not care to do intradermal tests in such sensitive patients. *Intradermal tests should be carried out with extracts which have proved negative by the scratch method.*]

Becker and Rappaport,[55] by the intradermal method, showed "a decrease in responsiveness to the injected allergen as one descends the forearm. The decrease in sensitivity varies directly with the distance down the forearm, with the rate of decrease independent of the concentration in the range of concentrations studied. The decrease between the uppermost and lowermost sites tested on the forearm is equivalent to approximately a 55 per cent decrease in strength of testing dilution. The radial side of the arm was found to be less sensitive than the ulnar, equivalent to approximately a 50 per cent decrease in strength of the testing solution." Zohn[568] found, like most of us, that skin tests with chocolate and cocoa are either negative or give slight reactions despite known clinical sensitivity. [The same is true of milk.]

COMPLICATIONS OF ASTHMA

Involvement of the nose and paranasal sinuses is so common as to be almost a part of bronchial asthma. Rawlins[408] states that allergy is the most common cause of chronic sinusitis; inhalants are usually responsible; the primary treatment should be directed at clearing the allergy, and any infection should be treated conservatively unless otherwise indicated; nose drops should be used with caution. Hyposensitization is used for those inhalants which cannot be avoided e.g. house dust, molds, tobacco smoke and paper. Injections should be stopped when the patient is comfortable; reinject if and when symptoms recur. Darrough[146] says that 75 per cent of rhinological practice deals with nasal allergy; infection may also be present. The allergy is diagnosed by the typical pale, edematous nasal membrane with profuse mucus and sneezing, plus eosinophilia. The presence of polyposis is positive proof of allergy. He never makes more than fifty skin tests for each patient, all intradermal.

Emphysema is almost always present in chronic asthma. Ornstein[369] notes that it differs from other pulmonary and cardiac diseases by impaired diffusion of oxygen and carbon dioxide between the alveolar air and the blood. He analyzed exhaled gases obtained in a 1-liter rebreathing bag in twenty seconds after a standard exercise test of stepping up and down an eight-inch step thirty times a minute. A residual oxygen volume up to 9.5 per cent or lower represents good diffusion of oxygen. Above 10 per cent indicates impaired permeability and diffusion. In addition to this test the ventilatory function is measured with a spirometer for one minute. In a case of lung hypertrophy which compensated for a shrunken, fibrotic, tuberculous left upper lobe healed with pneumothorax, the patient's pulmonary distress was due to poor ventilation; his ventilatory factor was 5.2 (normal 20). Yet his diffusion of oxygen and carbon dioxide was normal. Therefore the decreased ventilation resulted from the destruction of one lung; the hypertrophied right lung, after seventeen years of overactivity, was not emphysematous. Pulmonary function tests are especially important when such surgery as pneumonectomy is being considered.

Castex and his associates[574] produced experimental bronchogenic emphysema in dogs. They were able to reproduce the different stages observed in man, i.e. alveolar dilatation, anatomic emphysema, and ampullary emphysema. These different stages and grades depend more on the intensity of the respiratory obstruction than on the time of its evolution. The greater the obstruction the more severe is the resultant emphysema and the earlier the onset. In addition, the heart of the dog with the experimental emphysema is almost always enlarged, with right ventricular dilation.

Spontaneous pneumothorax is not uncommon in bronchial asthma but Myerson[352] found that asthma was the cause in only three of 100 cases seen at the Boston City Hospital in a nine-year period between 1934 and 1943. Since 375,000 patients were admitted to the hospital in that period, the incidence of spontaneous pneumothorax (all types and causes) was only 0.027 per cent. Of the 100 cases sixty-four, with an average age of forty-six, had some underlying pulmonary disease, of which tuberculosis constituted 59 per cent. Thirty-six cases occurred in apparently healthy persons, with recurrence in three patients, with an average age of only twenty-seven. The symptoms in both groups are about the same, chiefly chest pain and dyspnea. About 20 per cent of both groups gave a history of unusual exertion prior to the acute episode. Aspiration of air to relieve dyspnea was necessary in three cases.

Centrangolo's patient[108] had spontaneous pneumothorax which recurred during attacks of bronchial asthma. He therefore injected 3.0 c.c. Lipiodol and placed the patient on his right side so that the Lipiodol could enter the emphysematous-bleb part of the lung. Adhesions resulted, and although the patient continued to have asthma there has been no further recurrence of pneumothorax.

Dickie, in students seen during four years at the Health Service of the University of Wisconsin, observed twenty cases of spontaneous pneumothorax and pneumomediastinum (mediastinal emphysema).[155] There were six cases of pneumothorax without recognized mediastinal air, seven with mediastinal emphysema alone, and seven with both. In none of these was asthma a factor although an x-ray film suggested emphysematous blebs in one case. Recurrences were rather frequent, and aspirations of air were resorted to for dyspnea or for a prolonged course of symptoms. Dickie gives an excellent description of the symptoms in the fourteen cases with pneumomediastinum, with or without pneumothorax. The onset was usually sudden and varied in severity. Pain was usually "substernal with frequent radiation straight through to the back or into the left neck or shoulder. Pain is associated with change in position or with jarring motion, and six of fourteen patients with pneumomediastinum were aware of peculiar sounds over the precordium. On examination the most characteristic finding in this group is the crunching sound synchronous with the heart beat. This may vary greatly during the episode and with change in position or phase of respiration. The intensity of the sound bears no relationship to the severity of the patient's symptoms; often the patient is almost free of pain when the crunching is most pronounced." Subcutaneous air in the neck or elsewhere was not found in this series.

In a man of fifty-seven with asthmatic attacks for twelve years, Karns and Daue[276] found spontaneous mediastinal emphysema. Cough, pain and dyspnea began suddenly seventeen hours before admission, with swelling of the face and neck and increased dyspnea a few hours later. The face, up to the zygomatic arch, neck, left forearm, both arms, thighs, scrotum, chest and abdomen were ballooned up by subcutaneous emphysema. Crepitus was present and the trachea was deviated to the right; crackling sounds were heard over the precordium during systole and diastole.

Left pneumothorax was also present. The swelling and dyspnea were so extreme that mediastinotomy was carried out under local anesthesia, with escape of retained air and immediate improvement as regards the patient's cyanosis and dyspnea and recovery a little later.

In Klein's case[281] spontaneous pneumomediastinum with fever and leukocytosis occurred in a boy of sixteen. By a series of electrocardiograms right ventricular strain was shown, probably due to encroachment on the pulmonary arteries by air in the vascular sheaths. Subcutaneous emphysema occurred in an eighteen-year-old patient of Mascheroni and his associates.[335] The episode took place during her first attack of asthma. There was no pain and the emphysema disappeared in eight days. Air bubbles were easily demonstrated on x-ray. The authors discuss thirty-four cases previously reported as occurring during attacks of asthma.

Massive atelectasis (massive collapse) is rather rare in asthma [small areas of atelectasis are probably much more common than we can prove]. Huff[266] reports two attacks, complete in one episode, and incomplete in another. The seven-year-old child, with a history of asthma and perennial hay fever since infancy, was first seen in 1932. The massive collapse occurred suddenly in 1944, with shifting of the mediastinal structures to the affected side. Despite the x-ray findings symptoms were unbelievably mild, and there was no fever. She apparently coughed up a mucous plug because an x-ray film ten days later was entirely normal. A second attack occurred eight months later with partial atelectasis of the same side. She was treated successfully with aminophyllin, Adrenalin and inhalations of carbon dioxide.

Spontaneous fracture of a rib occurred in a fifty-nine-year-old asthmatic woman. The pain was on the right side of the neck but the x-ray film revealed a recent fracture of the left first rib. Violent contraction of opposing accessory muscles of respiration probably caused the fracture, says Ginsburg.[220] [We believe that the severe cough present in some asthmatic attacks is the cause and we have recently seen fractures in lower ribs in two of our patients. When one sees the terrific effort used by some patients to expel sputum one would expect even more fractured ribs. Incidentally, such a fracture is covered by accident insurance policies even though it results from asthma.]

Although *coronary* artery disease is infrequent below the age of forty, it caused death in nine of 365 consecutive fatalities, as disclosed by autopsies in an Army Hospital. Death was sudden in each case, says Poe[389] and coronary disease was the only factor. In discussing this case Abramson says "Myocardial disease is not considered to be an early complication of bronchial asthma. Unexpected and unexplained deaths in patients with bronchial asthma below forty are more frequent than is commonly believed. Closer scrutiny of myocardial function in bronchial asthma might reveal hitherto unexpected pathologic lesions in this group." [We do not subscribe to Abramson's opinion; coronary occlusion is uncommon before forty and is probably even less common in asthmatics, possibly because many such patients have learned that tobacco smoke irritates them. We are firmly convinced that heavy cigarette smokers are leading candidates for early occlusion.]

Cor pulmonale is thought by some to result from bronchial asthma as well as from other pulmonary disorders. Spatt,[487] in a study of forty-two cases with autopsy findings, confirms the theory that chronic pulmonary disease is the most important cause of cor pulmonale. The chronic condition destroys and narrows pulmonary capillaries and increases pulmonary artery tension which in turn increases the strain on the right heart; this in turn may result in dilatation and hypertrophy. A study of these forty-two cases disclosed that chronic exertional dyspnea, cough and cyanosis evidently reflected the first stage of the process. Later there followed distension of neck veins, hepatomegaly, edema, ascites and precordial distress. Cor pulmonale is more frequent in men, and death was most frequent between the ages of fifty-one and seventy. An editorial[127] also discusses cor pulmonale and quotes previous work by Scott, Spain and Handler, and Brill. Chronic obstructive emphysema is the main cause and other conditions are less frequent, these including silicosis, bronchiectasis, tuberculosis, bronchial asthma, silicotuberculosis, kyphoscoliosis, and pulmonary arteriolar sclerosis. [It is our impression that cor pulmonale rarely, if ever, occurs in uncomplicated bronchial asthma, no matter how severe, how chronic, or how emphysematous the patient becomes. Every case we have seen has some other condition which is the main or associated factor, e.g. bronchiectasis, kyphoscoliosis or pulmonary fibrosis or tuberculosis. We also believe that left heart failure is extremely rare in bronchial asthma unless the patient has some such associated condition as hypertension, chronic nephritis, aortic regurgitation or coronary occlusion.]

Pulmonary tuberculosis is not a complication of bronchial asthma but the two

conditions can be associated. Van Wezel[532] stresses the importance of controlling allergic bronchial asthma in patients whose tuberculosis needs collapse therapy. The type of collapse therapy will depend a great deal on prevention of attacks of bronchial asthma. He presents ten cases to illustrate the difficulties in the diagnosis of asthma in the presence of tuberculosis, the forms of surgical treatment necessary to control the tuberculosis, and the dangers of such therapy during attacks of asthma.

Cohen[120] reports that bronchial asthma occurred in fifty-five of 7,301 tuberculous patients discharged from Olive View Sanitarium in a ten-year period, an incidence of only 0.75 per cent (lower than that reported among the general population). These two conditions do not seem to predispose to one another although severe asthma seemed to be associated with serious endobronchial tuberculosis. In addition, there are fifteen cases in which the asthma and tuberculosis were present in patients still in the sanitarium. In thirty-eight cases the asthma preceded the tuberculosis and in six cases the reverse was true.

Zeuhn[567] also discusses surgical treatment in such cases. By having the patients high up in the mountains both conditions are so benefited that pneumothorax and thoracoplasty can be successfully carried out. In twenty-six cases of inactive pulmonary tuberculosis with bronchial asthma, Richard[411] obtained good results over a period of a year by injecting very minute dosages of tuberculin. There was no activation of the tuberculosis. Alemany Vall,[14] from Barcelona, contrary to American authors, finds pulmonary tuberculosis very frequent in asthmatic patients—from this he concludes that hypersensitivity to tuberculin causes the asthma, that tuberculin reactions are much more pronounced in these patients than in "simple" tuberculosis, that hypersensitivity to tuberculin causes typical allergic states such as eosinophilia, nasal polyposis, et cetera, before progressing to its usual fatal termination. Dugoujon and Mallet Rene[162] also support Jacquelin's thesis of the tuberculous origin of most cases of asthma, based on the frequency of old quiescent tuberculosis in such patients, of positive tuberculin tests, and of good results from tuberculin therapy. [Despite the higher incidence of tuberculosis in Spain and France as compared with our country one cannot agree that tuberculosis or sensitivity to tuberculin causes true allergic bronchial asthma; any good results from the treatment of bronchial asthma by injections of tuberculin are non-specific.]

Froman[200] has a nice paper on complications of arrested pulmonary tuberculosis. Bronchiectasis, emphysema, bronchogenic carcinoma, and/or atelectasis occur not infrequently in such cases, and the physician may wrongly believe that the tuberculosis has again become active. Wheezing and dyspnea may occur and thus suggest asthma. Kurkijarvi,[289] in a study of 200 cases of pulmonary tuberculosis, found slight eosinophilia in the blood and sputum in many of these. This may be confusing in instances in which asthma and tuberculosis coexist.

BRONCHIECTASIS

The relationship between bronchial asthma and bronchiectasis is still disputed. The two frequently coexist. Mallory,[331] in an authoritative study, summarizes: "Five factors—chronic bronchial infection, congenital abnormalities of the bronchial tree, bronchostenosis, pulmonary atelectasis and pneumonitis or its sequel, pulmonary fibrosis—have been shown to be potential factors in the etiology of bronchiectasis. Of these, congenital cystic disease and bronchostenosis are comparatively uncommon. Bronchial inflammation alone is rarely an effective factor but in combination with atelectasis or pneumonitis adequately accounts for most of the characteristic features of the disease."

Bronchiectasis has four important features: (a) it is rarely diffuse—it usually involves a group of adjoining bronchi; affected segments may be, and frequently are, multiple, but bronchi in uninvolved areas are normal. (b) It is not a progressive disease; there is no extension unless there occurs an attack of pneumonia with involvement of another segment of lung. (c) It is rare as an isolated finding in an otherwise normal lung; the surrounding lung tissue is abnormal, with atelectasis, fibrosis, organized pneumonitis, focal emphysema, or even destruction of alveolar tissue. (d) It usually develops in youth, though it can start at any age. Mallory points out that in bronchial asthma "functional narrowing of the bronchi exists over many years. In a group of sixty such cases that I have personally studied bronchiectasis was so exceptional that it appeared coincidental, although emphysema and cor pulmonale were of common occurrence. Stenosis of bronchi, therefore, does not regularly induce dilatation of the distal branches. If the obstruction is incomplete and expiration is impeded more than inspiration (as in asthma) the alveoli rather than the bronchi tend to dilate, and emphysema results. With complete obstruction atelectasis follows, and this is an important factor in the develop-

ment of bronchial dilatation. . . . It must be emphasized that it is not atelectasis per se that tends to dilate bronchi but the effect of the exaggerated negative intrathoracic pressure, which frequently follows atelectasis. In his fifty cases of bronchiectasis Mallory found emphysema in six but in only one was the emphysema an important cause. "The most hopeful prophylactic measure in the prevention of bronchiectasis is therefore the prevention or prompt alleviation of atelectasis."

Llaudet,[305] from Barcelona, says that congenital defects cause most cases of bronchiectasis; infection, especially tuberculosis, is the usual exciting factor; the prognosis is unfavorable, with resultant disability; hemoptysis is common and causes death in 5 per cent of the cases. Early lobectomy cures 94 per cent of the cases; medical treatment including aerosol is usually unsuccessful. Infante,[268] however, obtained excellent results from penicillin aerosol therapy in a five-year-old girl with saccular bronchiectasis, and success follows intratracheal injections of penicillin, says Thiberge[508] and Loesches.[309] Olsen[366] says resection of the affected portion of the bronchial tree is the best treatment but nebulization helps before lobectomy. When resection cannot be carried out, nebulization (penicillin and/or streptomycin) usually gives some relief, with relapse when inhalations are stopped. Overholt, Betts and Woods[371] discuss segmental resection, a procedure in which infected lung tissue is removed without sacrificing healthy parts.

Singer[472] discusses congenital and acquired bronchiectasis, with tuberculosis the most common cause. Spencer and Kent[488] believe bronchiectasis is next only to tuberculosis in frequency of chest diseases and is often misdiagnosed. It usually begins in childhood, probably following bronchial infections, whooping cough, asthma, pneumonias, measles, scarlet fever, and lung abscess. Sinus disease is a factor. In a photoradiographic survey of 156,000 candidates for flight training, Steinhausen and Fine[491] found forty-one cases of unsuspected bronchiectasis. Wearing[554] reports forty-six cases of bronchiectasis in 214 patients whose symptoms suggested chronic bronchitis, with a past history of pneumonia in twenty-six. Clubbed fingers were present in eight cases, and Poppe[392] says clubbed fingers occur in about 80 per cent of cases with severe bronchiectasis and chronic lung abscess.

Surgical aspects of bronchiectasis are discussed by Naef,[354] Allan,[10] Streider,[498] and Valledor and Rodriguez Dias.[525] Badger[44] points out, however, that in 400 cases of bronchiectasis treated in the Massachusetts General Hospital, 59 per cent were unsuitable for surgical treatment. For these and for those who refuse surgery or have little or no symptoms, medical management is necessary, e.g. mechanical drainage, control of infection, measures to improve the general health and the prevention of bronchiectasis. Biering[65] and Averbe[41] also discuss this condition, and Schmidt,[445] Gann,[213] Dell[151] and Blaisdell[71] give the technique and indications for bronchography.

Carr, Denman and Skinner[102] report that forty-six of 144 workers in a gas (mustard) shell loading plant developed moderate to far advanced bronchiectasis, with minimal symptoms in forty-one or more. Asthmatic bronchitis was present in forty patients, and eleven had bilateral emphysema. By removing these patients from contact with mustard gas, plus medication, good results were obtained in almost all cases except in those with emphysema.

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

When a patient is referred for "asthma" we must prove that bronchial asthma is or is not present. We have recently had cases in which the "asthma" was due to sighing dyspnea, substernal thyroid, carcinoma of the trachea, cardiac disease, or silicosis. The differential diagnosis and management of bronchial asthma is outlined by Unger,[523] along with a table giving the differential points between bronchial asthma and "cardiac asthma," also a discussion of two patients with asthma and another one whose dyspnea was due to byssinosis, a condition akin to pneumoconiosis. This patient stuffed loose, raw cotton into quilted robes and inhaled some of the cotton. X-ray films revealed a diffuse mottling throughout both lungs, due to fibrosis, and the patient had fever for about a year.

Sweany and Thompson[502] outline laboratory methods useful in the differential diagnosis of chronic chest diseases, e.g. the sedimentation rate, the increase in serum globulin so characteristic of sarcoidosis, the differential blood count (often neglected) cultures of the sputum, stomach washings, pleural fluid, bronchial aspirations, biopsies, animal inoculations, micro-sections, and skin tests with tuberculin, histoplasmin and coccidioidin. Smart[176] and many others emphasize the importance of mass chest surveys of apparently healthy groups, chiefly to pick up cases of pulmonary tuberculosis.

Adenoma of the bronchus is not rare and may cause dyspnea and wheezing

and thus be confused with bronchial asthma. Naclerio and Lange[353] find this tumor in about 80 per cent of the benign bronchogenic growths. Symptoms are rare at first but a dry, irritating cough follows. Hemoptysis is a cardinal symptom, and symptoms from partial or complete obstruction of a bronchus may or may not occur. The diagnostic procedures include plain and section roentgenography, bronchography and, best of all, bronchoscopy. Ten patients were cured by pneumonectomy and five by lobectomy. Souders and Kingsley[181] review the literature and present fifteen cases of their own; these were found among 217 histologically proved primary lung tumors encountered at the Lahey Clinic since 1930, an incidence of 6.9 per cent. Adenomas can usually be diagnosed bronchoscopically; they are potentially malignant but the malignancy is of low grade. Sixty per cent occur in patients less than forty years old. Resection of the tumor and infected lung tissue is advised but pedunculated adenomata may be removed alone. Fried[191] also emphasizes that a bronchus adenoma is benign, occurs in bronchi whose diameter is at least 10 mm., grows into the lumen or the parenchyma of the lung, and may cause cough, wheezing, hemotypsis, and recurrent symptoms like pneumonia if obstruction occurs.

Holinger, Andrews and Anison[262] discuss pulmonary complications due to *endobronchial foreign bodies*. "In a series of 1026 consecutive cases of foreign bodies in the air and food passages (in eleven years), 353 or 32 per cent were found and removed from the tracheobronchial tree. Pulmonary complications depend upon the location, sojourn, and character of the foreign body. Vegetable objects (peanuts, corn, beans, twigs, grass heads, etc.) produced the most severe acute inflammatory processes and were often overlooked as the cause of the disease. Metallic objects (tacks, screws, parts of toys, safety pins and common pins) were not as frequently the cause of severe acute pulmonary infections, but were more often responsible for extensive bronchiectasis, severe hemoptysis, empyema, and pneumothorax when they remained in the bronchi for weeks, months or years. . . The individual complications consisted of 'asthma,' emphysema, pneumothorax, atelectasis, bronchiectasis, lung abscess, and empyema. Two fatalities (0.6 per cent) in the 353 cases of bronchial foreign bodies are recorded." They emphasize the importance of a careful history and examination, including x-ray and endoscopy. A history suggesting foreign body is invaluable but a negative history is valueless and misleading. Early discovery and removal of foreign bodies lessen serious complications.

Peanuts are especially dangerous. Bonnier[77] removed them from the lower respiratory passages of forty-five patients (forty-three children), with death in five cases. Ages in children ranged from eight months to ten years. In thirty patients (66 per cent) there was a definite history of choking on a peanut. Three out of four peanut kernels were found in the right bronchus, with only seven found in lower lobe bronchi. A child's life is endangered when it is very young, or when the peanut is large or obstructs high up; in such a case death can be quick. A small piece low down can give few signs and symptoms occur more slowly. In many of the cases the x-ray films did not show the peanut even when present. The symptoms are not always classic. Only a slight cough or wheeze may occur, but an "asthmatic wheeze" was present in almost every case. Huff's 3-year-old child[265] wheezed on expiration for six months. A tentative diagnosis of bronchial asthma was made, but removal of a long roofing tack from the right main bronchus solved the case. Edema of the walls of the bronchi and tenacious exudate around the tack simulated bronchial asthma.

Tumors of the lung are discussed by many. Pool[391] discusses carcinoma and emphasizes the importance of such symptoms as hemoptysis, cough and pain, and the findings of consolidation, atelectasis, and/or localized emphysema or pleural effusions. Wheezing or persistent rhonchi over one area is always suggestive of partial bronchial obstruction, especially when associated with prolonged expiration. If these findings are repeatedly present a growth is probably present, not a mucous plug.

In addition to those papers already discussed in the section on bronchiectasis, Clerf[117] notes progress in the science of bronchology. Less than 2 per cent of all bronchoscopic procedures are now performed for foreign bodies, as compared to about 25 per cent in earlier years. Bronchopulmonary diseases, including bronchial asthma, now far overshadow foreign bodies as causes for bronchoscopic study and therapy. In addition to its value in differential diagnosis of asthma, Clerf correctly says "studies of fatal cases of status asthmaticus have shown that one of the most common and important causes of death is the blocking of the larger air passages by thick, tenacious secretion. Failure to secure a satisfactory response by the accepted methods of medical treatment in cases of marked dyspnea due to accu-

mulated secretions necessitates that these be mechanically removed by bronchoscopic aspiration. Spectacular results have been secured at times in moribund patients. It is obvious, of course, that in cases of this type little can be hoped for unless the life-saving measures are employed by one well qualified; for among bronchologists it is admitted that two contraindications to bronchoscopy are an inadequate armamentarium and a poorly trained bronchologist." [We say "Amen"] we at Wesley Memorial Hospital are fortunate in having the services of an excellent bronchoscopist for both diagnosis and treatment. We are sure that he has saved the lives of several of our patients.]

Broyles[91] discusses bronchoscopic experiences with tumors of the lower respiratory tract. Holinger[261] points out that both bronchial asthma and emphysema may closely simulate other diseases in which bronchial obstruction occurs. Even more significant is the frequency with which a true obstruction is considered simple bronchial asthma. The confusing factor is usually the "asthmatoid" wheeze caused by the obstruction, yet it differs from the wheezing in bronchial asthma because in the latter cough usually changes the wheeze and the wheeze is usually louder on expiration. The wheeze of obstruction is uninfluenced by cough and is usually inspiratory. Bronchoscopic examination usually helps in differentiation. Holinger's endoscopic photography in this and related fields should be seen by all.

Epstein, Sherman and Walzer[175] note that bronchography may be greatly facilitated by injections of epinephrine. In sixteen asthmatic patients attempts at bronchography without epinephrine were unsuccessful. Spasms of cough occurred as iodized oil was instilled and the oil was either expectorated or swallowed; under fluoroscopic observation no oil entered the swollen bronchi. But when 0.5 to 1.0 c.c. of 1:1000 epinephrine was injected subcutaneously the secondary bronchi relaxed within thirty seconds and the oil could be seen entering and outlining the bronchial tree. Little discomfort occurred, and good grams were obtained in fifteen of these sixteen patients, with radiologic evidence of bronchiectasis. The entire technique of the procedure is outlined.

TROPICAL EOSINOPHILIA, LOEFFLER'S SYNDROME, PERIARTERITIS NODOSA

Confusion still exists in differentiating these three conditions. Eosinophilia is usually much higher than in bronchial asthma. Wheezing and dyspnea are often present.

As noted in our last review[521] Wilson[559] found seven cases of *tropical eosinophilia* in East Africa in thirty-four natives with chronic cough or wheezing. All were sick less than three years, and all had leukocytosis with pronounced eosinophilia. Six were completely relieved by intravenous injections of arsenic; one cleared spontaneously. Symptoms usually continue until the specific arsenical is given, whereas in Loeffler's syndrome the cough, fever, eosinophilia, leukocytosis, and pulmonary consolidation usually clear spontaneously in about eight days. Wilson therefore does not believe the two conditions are the same. Coutinho,[131] from Brazil, reports five cases of tropical eosinophilia. In two there seemed to be a relationship with infection (amebiasis). As previously stated[54] Telles[507] gave the first report from Brazil.

Loeffler's syndrome continues interesting. Loeffler, who first described the syndrome (1932), and his co-workers[307,311] say that the picture of transitory lung infiltration, with fleeting blood eosinophilia, is benign. Ascaris infestation is the main cause, they say, and in their cases Ascari were found in the intestinal tract in 23 per cent and within 4 to 6 weeks after the lung infiltration became manifest. Other factors are rarely responsible. In forty-eight guinea pigs they demonstrated the causal significance of ascariasis. They reproduced in every detail the syndrome of evanescent pulmonary infiltration, and demonstrated the larvae of Ascaris in eosinophilic infiltrations, thus confirming observations made by von Meyenburg and Nagel in the human. They emphasize atelactasis as a cause of the infiltrations.

Von Heni and his associates[539] review fifty-six cases, forty of which occurred in about a year. Their work with animals and patients confirms the importance of Ascaris infestation. The outlook in all cases is good, and the treatment is "worm cure." Clark and Rosenberg[115] studied a four-year-old boy admitted to the hospital because of a second tonic seizure of the upper extremities. There was no history of allergy, and blood eosinophilia was 4 to 12 per cent. X-rays showed typical migratory lesions. Ova of Ascaris lumbricoides and Trichuris tricuria were found in the stools, a skin test was positive for Ascaris, and anthelmintic treatment was followed by improvement after four weeks.

Bertrand-Fontaine and associates[64] report two cases in young women, both severe, with widespread pulmonary involvement. Two months after onset Ascari were

found. The authors believe that the pulmonary manifestations result from the direct action of the worm in its migratory stage in the lung; they do not think the condition is allergic, not even to Ascari at distant sites. This concept is supported by the facts that (a) larvae are not found in sputum during acute pulmonary symptoms; (b) in the two cases cited the recovery of adult Ascari in the stools coincided with the expected time in the life cycle after the pulmonary migration.

O'Byrne[363] says Loeffler's syndrome is almost certainly an allergic phenomenon. While infestation by Ascaris is important in many cases, it cannot be the sole or even the main cause, at least in this country. Pollen, bacteria, viruses, amebae, and other factors may be responsible. In O'Byrne's 5-month-old girl the eosinophilia ranged from 4 to 50 per cent. There were no respiratory symptoms at that time, but in the last seven years there have been occasional attacks of asthma. The case report contains six excellent roentgenograms.

Ham and Zimdahl[234] review the literature and add three cases. One had a long, stormy course which did not resemble typical Loeffler's syndrome. In another, symptoms suggested angina pectoris. Only the third patient had a definite hypersensitive background and in none was the cause found. Squier[489] also reports three cases. In one of these, early fleeting infiltrations occurred but repeated attacks have left increasing residual fibrosis and evidence of irreversible damage. This irreversibility seems more common in so-called intrinsic or bacterial sensitivity. Single cases are reported by Pearlman,[375] Williams and Walker,[558] Rice and Scott,[413] and Dallas.[143] In a forty-two-year-old patient of Henderson and Pierce,[250] the usual transitory shifting pulmonary shadows and pronounced fluctuating blood eosinophilia were present. In addition to sensitivity to house dust and ragweed pollen, the patient was also allergic to the infecting organism, Hemophilus influenzae, which was constantly found in the sputum and infected sinuses. Later, on readministration of the specific vaccine, there developed joint and muscle pains, fever and purpura of the Schönlein type, and a transitory bundle branch block. This indisputable evidence of vascular allergy corroborates the view that the Loeffler shadows are due to allergic edema of the interalveolar pulmonary tissue with its widespread capillary connections.

Font[189] considers Loeffler's syndrome merely a variation of tropical eosinophilia. Wheezing occurred in his second patient, and both patients had transient pulmonary infiltrations and high blood eosinophilia. He attaches much importance to the fact that he isolated pure cultures, chiefly streptococcus viridans, from sinuses of both. A case reported by Elkeles and Butler[173] is unusual in that a 19-year-old soldier showed a transient apical cavity as well as recurrent pulmonary infiltrations, along with eosinophilia in blood and sputum. There was no tuberculosis. The great variety of antigens causing this syndrome indicate that it is not a specific entity but rather a manifestation of allergy in which the lungs are the main shock organs.

Interesting are five case reports by Diaz Rivera and associates.[154] Because of eosinophilic infiltration of the lungs he makes the diagnosis of Loeffler's syndrome—yet rapid and striking improvement followed therapy with arsenicals. [Here, then, we see further reason for the confusion which exists in nomenclature. Arsenicals are practically specific in tropical eosinophilia, not in Loeffler's syndrome. Such reports as these emphasize the close relationship of these two diseases.] Berman[59] discusses Loeffler's syndrome in children, and Pedrazzini[375] finds that the most frequent cause is intestinal taenia. De Martini[152] differentiates lung cysts and Loeffler's syndrome; he believes that tuberculosis is usually responsible for the syndrome. Lehmann[293] has an interesting paper with a case report of a man with both Loeffler's syndrome and erythema multiforme. He reviews the literature on the syndrome, tropical eosinophilia, creeping eruption, and eosinophilic granulomas of the skin. He also tabulates the causes of eosinophilia.

Periarteritis nodosa is reviewed by Laipply.[290] The entire thickness of vessel walls may be affected. Localized thickenings of arterial walls with aneurismal formations may lead to nodular swellings (nodosa). Hemorrhages ranged from petechiae to extensive. Rupture of aneurisms may be fatal. Microscopically: there is edema, degeneration, necrosis, exudation in all coats of the vessels. Clinically: there are two groups: (a) those with an acute infection with toxemia, and (b) those with circulatory disturbances from the arteritis, depending on involved sites. Course: this is usually fatal, but recoveries have been reported. Duration: this is from weeks to months, infrequently years. Etiology: this is unknown; allergy thought to be a factor.

Goodman's 17-year-old patient[226] recovered after an attack of periarteritis nodosa which probably was due to ingestion of 4 grams daily of sulfadiazine for about a week, given for a sore throat. Recovery occurred but the sore throat returned

in six weeks, and after another two days of sulfadiazine he became very ill and stopped the drug. Fever, purpura, prostration, and other symptoms followed. Biopsy of the deltoid muscle showed periarteritis nodosa. The boy was very toxic and a house physician, apparently unfamiliar with the patient's history of sulfonamide sensitivity, resumed therapy with sulfadiazine, one gram daily. Generalized urticaria developed, relieved by epinephrine and the diazine was continued for five days. Improvement and recovery, strangely enough, followed. Skin tests two years later were negative, and no clinical symptoms followed ingestion of 2 grains of the diazine. In this case recovery seemed to follow a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness.

A 51-year-old female patient of King[282] is still living after symptoms for perhaps ten years. Since her discharge from the hospital her weight has increased from 93 to 129 pounds, with no fever for about a year. But blood eosinophilia and tender skin nodules persist. Asthmatic symptoms and chronic sinusitis preceded the onset of the periarteritis nodosa. No definite etiologic factor other than allergy was found.

Recovery is reported by Miale, Doege and Piehl[340] in a 40-year-old man, despite gangrene of the ileum, acute renal damage and allergic dermatitis. The arteritis was diagnosed early and medication was stopped, with recovery. A second patient, aged sixty-seven, showed marked periarteritis nodosa on autopsy, with most severe involvement in the kidneys and liver. The authors are sure that the relationship between hypersensitivity and acute arterial disease is more than accidental. Definite atopy was present in both men. Madison[329] discusses the pathology of this condition and three cases in which the occurrence of hemorrhage was invaluable in early antemortem diagnosis. In Case 1 the bleeding was into the skin and from the lungs and intestines; the lungs and stomach were involved in Case 2, and the stomach, skin and kidneys in the third patient. A 62-year-old male patient had no allergic manifestations until twelve months before his final illness, say Shepard and Phillips.[328] Then "asthma" occurred, followed by serosanguinous nasal discharge, profuse perspiration, pain, paresthesias, eosinophilia, wasting and terminal hemoptysis; autopsy confirmed an earlier diagnosis of periarteritis nodosa.

PULMONARY DUST DISEASES

Diseases due to inhalation of various dusts must also be differentiated from bronchial asthma. *Silicosis* is discussed by several writers. Yegge[565] says roentgen supervision is necessary for all exposed. Susceptibilty is increased if ciliated epithelium has been injured by infection. The hazard of silica dust varies with size of particles, number per cubic foot of air, free or combined state of silica, humidity, and length of exposure. Engineering control is best, but difficult and expensive. The most harmful particles are 1 to 3 microns in diameter; those over 10 microns have no effect. [This fact is also pertinent in the size of particles used in aerosol therapy, as with penicillin.] Damage begins when dust containing 70-80 per cent silica exceeds 5,000,000 particles per cubic foot. The risk of complicating tuberculosis is increased with excessive humidity. Dyspnea, cough, expectoration, bronchitis, and emphysema are common, thus simulating asthma. Death usually occurs from tuberculosis or rather sudden cardiac decompensation. Yegge likes Garland's classification of silicosis: incipient, interstitial, nodular, and conglomerate.

Yegge says that aluminum hydrate directly inhaled or dispersed in dressing rooms before exposure may inhibit the pulmonary effect of silica. Berry,[63] in a study of twenty-six silicotic patients who were treated with inhalations of aluminum dust and nine patients who received no aluminum, could find no definite difference between the two groups. Most of the patients in both groups reported subjective improvement. But there is evidence that the treatment itself may be harmful;[20] aluminum in certain physical states may cause pneumoconiosis. Dernehl[153] favors the aluminum treatment of silicosis; there are now 102 treatment units in the United States with a high percentage of reported improvement. He believes that the pulmonary symptoms in silicosis are due to bronchospasm, not to toxicity.

Roche and Ode,[422] in the Lyon-Saint Etienne district of France, state that the emphysematous lesions accompanying silicosis can be strikingly demonstrated by a post-mortem radiologic technique. They believe that the severe dyspnea, out of all proportion to the clinical x-ray evidence, and the inefficiency of treatment are due to extensive emphysema. In Switzerland, says Nicód,[360] exposure sufficient to cause silicosis may vary from a few months in a mine to as much as thirty-four years. In 100 miners, seventy-seven exhibited their first symptoms less than ten years after they quit the mines, whereas twenty-three others lived a nor-

mal life for more than ten years in a dust-less environment before dyspnea and bronchitis occurred. Tuberculosis occurred in seventy-one of 117 cases.

Byssinosis (inhaltation of cotton) is mentioned above by Unger,[523] and Dernehl[153] says repeated prolonged exposure in cotton workers causes chronic irritation of the respiratory tract, with "asthma" in some. Allergy to cotton protein may occur, as proved by direct skin tests and by passive transfer.

Bagasse lung disease may not be due to inhalation of particles of bagasse fiber (sugar cane from which the sugar has been extracted) say Gerstl, Tager and Marinaro.[218] Lesions in experimental rabbits did not resemble human bagasse disease nor silicosis. Bagasse is stored for months to years, broken and pressed into such building materials as Celotex. It is thought that fungi cause deterioration of the fibers and that inhalation of these fungi causes the disease. Le Mone and his associates[291] point out the seriousness of the condition. About two months of exposure are required before symptoms occur, with fever, severe dyspnea, persistent cough, scanty mucoid sputum, and profound weakness. The onset is insidious. The exact etiologic basis is obscure although it occurs only in exposed persons. Radiologically, diffuse infiltration and consolidation, acute bronchiolitis or pneumonia may occur, but, fortunately, the condition is reversible, with resultant resolution and return to normal, provided, of course, that exposure is terminated.

Beryllium caused delayed pneumonitis in twelve men and twenty-four women who manufactured fluorescent lamps, says Hardy.[243] The material used to coat these tubes is a mixture of zinc, manganese and beryllium silicate. Onset of symptoms is gradual, with weight loss, fatigue, increasing exertional dyspnea, anorexia and nervousness. The dyspnea may become ceaseless, and in two the diagnosis was confirmed by autopsy. Of the thirty-six patients, twenty-three are still functionally disabled, twelve completely and eleven partially, and this after an average illness of two years. There is no satisfactory quantitative test for this chemical in the air, but the disease developed in two persons who lived close to the building where the fluorescent powders were being handled; they did not work in the plant. Pascucci[374] discusses the clinical, autopsy and radiologic findings in thirty-two patients. No other disease produces the characteristic fine, disseminate, granular type of infiltration of the lungs, as shown by x-ray. Both the granular and the nodular types may occur, and the prognosis is worse in those with the granular type of nodulation, especially when confluent shadows are superimposed. Roentgenologic changes, however, may exist without significant symptoms.

Siderosis (caused by inhalation of iron fumes) is a rather benign form of pneumoconiosis, with deposits of the metal dust in the lungs. Sander[442] reports three cases with (a) discrete and rather sharply defined rounded shadows of more or less uniform size and equal distribution in both lungs; (b) no tendency to confluence; and (c) hilar shadows always smaller than would be expected with silicosis of this degree. Gross black pigmentation at necropsy has been erroneously diagnosed as anthracotic, whereas a ferrocyanide stain would have revealed iron. Gross round lesions also have been incorrectly called silicotic without use of the connective tissue stains to determine true fibrotic nodules.

Asbestosis, another pulmonary inhalation disease, is discussed by Riddell.[415] It is due to fibrous silicate and lung fibrosis may occur, with a ground-glass appearance on x-ray. Cardiac symptoms are common. Riddell also states that inhalations of *Cadmium* (fumes or dust) can cause severe damage, with dyspnea, persistent cough, cyanosis, and prostration; a chemical pneumonia can occur. Lung disease can also occur from inhalation of *arsenic* and certain *radio-active substances*. Riddell discusses the factor of compensation in pneumoconiosis. Dernehl[153] says inhalation of *sulfur* is a rare cause of industrial disease in the United States, and the incidence of tuberculosis in *cement* workers is only 0.18 per cent as compared with 1.0-1.5 per cent in the general population; the general health in the cement industry is very good, and silicosis occurred in only six of 1,979 workers.

PULMONARY CYSTS AND BULLOUS EMPHYSEMA

These two conditions, perhaps the same, may be confused with bronchial asthma. Adams[7] has a fine article on the pathologic characteristics and importance of congenital lung cysts, based on a study of twenty-seven patients, in twenty-four of whom symptoms occurred only after the cysts had become infected. In several cases treatment for over a year had been carried on for other conditions, e.g. bronchiectasis, lung abscess, empyema, or tuberculosis. Nine other authors have reported similar experiences in twenty-six collected cases. Diagnosis is difficult because of similarities in the clinical course. The x-ray, with fluoroscopy, remains best for correct diagnosis, but must be correlated with the clinical findings. Since

the risk of operation is small, resection of the involved lung is the treatment of choice.

Solitary lung cysts were removed by Anderson[23] in twelve patients, with death in three; the survivors remain well. McRae[321] reports death from congenital lung cysts in four of eleven children in a French-Canadian family. This family incidence is unique, in that marked clubbing of fingers and toes occurred without pulmonary sepsis, yet the four children succumbed early in life. Ashen-grey pallor, without actual anemia, was present; cyanosis did not occur; dyspnea on exertion, frequent "colds" with cough and sputum and râles were present. Expiratory wheezing was widespread in one case, with the diagnosis of lung cyst confirmed by autopsy. Wheezing may dominate the picture so completely that nothing else can be made out. But repeated x-rays reveal steady progress of the cystic nature of the condition.

Korol[287] believes emphysema is a form of lung atrophy due to inadequate blood supply. Post mortem the anemia is striking, and histologically there is an obvious disappearance of capillaries. In a study of 100 cases of advanced bullous and cystic types of emphysema, allergic bronchitis and asthma were present in twenty-three cases, with progressive [illegible] occurs in the bullous type, says Korol, but not in the cyst[illegible] reports two cases of giant bullous emphysema in upper lobes. In one case great improvement followed lobectomy. Two cases of bullous emphysema associated with asthma and tuberculosis are reported by Lowance and associates.[314] They also discuss the differential diagnosis of bronchial asthma from asthma complicated by an omental hernia through the foramen of Morgagni into the right lung between the first and second lobes; intrinsic asthma with a superimposed cardiac asthma; and carcinoma of the lower bowel and wheezing due to metastases to the lungs.

FUNGUS INFECTIONS OF THE LUNG

These are probably much more common than we can prove. Smith[478] differentiates between coccidiomycosis and histoplasmosis. The skin tests are usually accurate, and identification of the respective fungus clinches the diagnosis. Dickie and Clark,[156] in a routine survey of 5000 students by photofluorograms and by tuberculin testing, found pulmonary calcification and negative tuberculin tests in 160. In sixty-six of seventy-three of this group this calcification was associated with postive skin tests to histoplasmin. It is therefore evident that a diagnosis of tuberculous infection made solely by x-ray is frequently wrong. Histoplasmosis can cause both calcification and infiltration.

In ten of seventeen patients ill with pneumonia in Camp Gruber, Oklahoma, Mickle[342] was unable to identify the cause. In ten of these C. Albicans was isolated but there was no other evidence to support its etiologic role. Moody[349] reports death in a Mexican laborer admitted for pulmonary tuberculosis, but with negative sputa. On bronchoscopy a fungating tumor mass was found below the larynx. Sections of cystlike masses and smears of mucinous bronchial material contained many encapsulated organisms characteristic of Cryptococcus neoformans (Torula histolytica). Autopsy was negative for tuberculosis; areas of silicosis were found. Penicillin and sulfonamides failed to help. Kay[278] writes on actinomyces in bronchopulmonary infections. The organism itself is commonly found in such infections (found in the sputum of 109 of 240 patients). Actinomyces were always found in mixed infection, but are probably clinically significant only under anaerobic conditions.

MISCELLANEOUS CONDITIONS WHICH MAY CONFUSE

Riley has a nice differentiation between cardiac and pulmonary dyspnea, one of a series of pamphlets published by the American Heart Association.[416] "Dyspnea is a manifestation of ventilatory insufficiency which may be caused by certain types of pulmonary or cardiac disease. A reasonable estimate of the contributions of each disease to the dyspnea can be made on the basis of characteristic physiologic abnormalities." He discusses the clinical symptoms of each, and various tests. In cardiac asthma, says Chapman[109] the râles are usually inspiratory, in bronchial asthma usually expiratory and sibilant. In bronchial asthma the entire costal margins move medially on inspiration; in cardiac asthma the median costal margin moves medially and the lateral ones laterally. Bizzozero[68] says cardiac dyspnea cannot always be differentiated from bronchial asthma. Crystal, Edmonds and Betzold[139] report a case with a symmetrical *double aortic arch*. The vascular rings encircle the trachea and esophagus and cause difficulty in respiration and in deglutition; there is a fairly characteristic syndrome with stridor, wheezing, crowing, bouts of cyanosis, dysphagia, regurgitation and recurrent respiratory infections.

The patient was eight weeks old, with wheezing and dyspnea since birth. There were periods of unconsciousness lasting from thirty seconds to ten minutes. Convulsions occurred at the age of ten, with distention of superficial veins of the neck and torso. The correct diagnosis was made, aided by the x-ray, but the child died during the operation; right and left aortic arches tightly embraced the trachea and esophagus.

Bishr's[67] ten-year-old boy had a huge right-sided pulmonary hydatid cyst which caused spasms of cough, dyspnea and wheezing, with some relief from ephedrine. There were 15,200 leukocytes with 14 per cent eosinophiles; the eosinophilia, however, lost most of its significance when ascaris ova were found in the stools. The Casoni skin test, using fresh fluid from a hydatid cyst, was strongly positive, and the sac was shelled out with no further asthmatoid attacks. No one knows exactly why this cyst led to attacks of "asthma."

Villafañe Lastra and his associates[536] describe patients with brucellosis in whom asthmatic symptoms occurred, varying from recurrent mild crises to severe status asthmaticus. When the diagnosis of brucellosis was established, aided by a Huddleson positive reaction and strongly positive intradermal reactions to Melitin, injections with Brucella abortus vaccines relieved the respiratory symptoms. The authors believe that a possible hapten of the Brucella toxin combines with pollen, dusts or foods to cause sensitization. They recommend routine investigation for Brucellosis, in addition to the usual allergy tests.

Becker[56] suggests that "heaviness of the chest" and/or a chronic cough may precede true asthma. In such cases the family history, eosinophilia, and relief from such drugs as epinephrine or ephedrine will aid in the correct diagnosis. Bernton's[61] seventy-seven-year-old female patient sought relief from an allergist because she had acute attacks of nocturnal dyspnea along with generalized hives, duration four years. Slight wheezing was noted. Skin tests had been carried out at the onset, were positive for house dust, and she had received aminophyllin and epinephrine. Significantly, she said, she had a "clutching feeling" below the left breast after dinner was down only a minute. An x-ray revealed that the esophagus was deviated toward the right in its lower third due to a large hiatal hernia of the stomach. Because of her age, operation was not carried out. Bernton says no real asthma existed but the dyspnea was almost certainly due to direct pressure by a distended stomach on lung tissue. Small, frequent meals were prescribed.

"Asthma" following a primary carcinoma of the pancreas is reported by Swiegert, McLaughlin and Heath.[503] At autopsy two months later this twenty-two-year-old patient showed diffuse metastatic involvement of the lungs, bronchial lymph nodes, liver, adrenals and vertebrae. Walker and Gann[546] report two cases of edema of the larynx complicating epidemic parotitis (mumps); such an occurrence may be confusing.

Neurocirculatory asthenia (effort syndrome) may lead to tachypnea and dyspnea, probably due to some essential irritability or stimulation of a center or centers within the central nervous system, this causing respiratory manifestations. Friedman[170] describes a new hyperventilation test, preceded and followed by maximal breath holding. The range of the H. I. (hyperventilation index) is about the same in normal persons and in patients with intrinsic pulmonary or cardiac disease, but without neurocirculatory asthenia. But those with this asthenia, with or without cardiorespiratory disease, always have a low H. I. Friedman discusses sixteen patients with respiratory symptoms due to hyperventilation. Attacks begin when the patients feel they are not getting enough air; so they breathe deeply and rapidly with a sigh during expiration; this leads to tachycardia and, in some cases, extrasystoles may occur. The hands and feet are usually cold and tremulous; excessive perspiration is common, along with vertigo, sharp precordial pain and tingling of the hands and feet. Carpopedal spasm occurred in three cases. Friedman emphasizes the fact that attacks can and do occur at rest, not always due to effort. [This is an important diagnosis, similar in many ways to "sighing dyspnea," but with an even greater psychic involvement. We have seen similar cases in which wheezing and dyspnea occur in patients who have a strong emotional personality; in such cases search for causative allergens is almost always ineffective even though their wheezing strongly suggests bronchial asthma. Relief occurs solely from psychotherapy. A recent example is a man who has been under our care for "asthma" for over a year. His attacks of dyspnea and wheezing were relieved by epinephrine and aminophyllin but he lost weight, morale and strength till he became an invalid and was dependent on his wife. Separation from his wife by transfer to a sanitarium has effected a remarkable improvement with almost total disappearance of his "asthma." In other words, this man probably never had real bronchial asthma—he had psychogenic symptoms for over a year.]

first period of treatment, until later he discovers that the new methods are not so fundamental after all.

"New treatments are always welcomed, but none of us can afford to believe at the onset that they are perfect. They deserve to be considered carefully and used with as much intelligence and care as possible. If the controls are good, if other cases treated with placebos do not do just as well, then the truth will appear.

"New theories are essential to our progress. If the theory is good, the evidence in support of it will become readily apparent and available. If, however, the theory is not so good and the evidence behind it is of doubtful value, then the further consideration of it is a waste of time. Ideas are valuable. No advances are made without them, but where the evidence is lacking or where the observations made can be explained quite as easily on some more familiar basis, publication should be withheld. When the evidence can be clarified and displayed in orderly fashion, then progress is made."

Gilman[219] discusses some of the drugs used in allergy, especially the mimetic and so-called lytic drugs. The chemical mediator for the sympathetic nervous system is sympathin which may or may not be chemically identical with epinephrine.

Likewise, the important parasympathomimetic drugs resemble acetylcholine in structure. "Epinephrine is a rather paradoxical drug in that it possesses two types of action, one excitatory, the other inhibitory." The first action causes contraction of smooth muscle, e.g. on musculature of blood vessels to effect arteriolar and capillarly constriction; this constriction of blood vessels of an edematous bronchial mucosa is very desirable as it lessens edema. Unfortunately, this excitatory action on blood vessels is often followed by a prolonged inhibitory action, e.g. after-congestion of mucosa, and in the long run capillary dilatation may occur rather than constriction; this may be the reason for "adrenalin-fastness." The inhibitory action of epinephrine causes relaxation of smooth muscles, both in the alimentary tract and in the bronchial tree, thus increasing the size of the lumina and lessening dyspnea.

Gilman points out that German investigators some six or seven years ago have largely eliminated the excitatory effects of epinephrine and increased the inhibitory action. Isuprel (Aleudrin) is one of these new compounds, made by substitution from the epinephrine structure. It causes a fall in blood pressure rather than a rise; it relaxes bronchi better than does epinephrine, but it does not constrict blood vessels nearly as well as epinephrine. Only prolonged clinical trial will determine the efficiency of Isuprel as compared with epinephrine.

Gilman says the term "antihistamine" drug is a poor one. Epinephrine itself is one of the best of the antihistamine drugs because it is a physiologic antagonist to histamine: histamine dilates peripheral vessels and constricts smooth muscle in the bronchi, epinephrine constricts these vessels and dilates bronchial muscles. The new antihistamine drugs act by blocking; they are not physiologic antagonists of histamine. Their action is similar to that by which atropin can block the effects of acetylcholine or of cholinergic nerve impulses. The term "histaminolytic" would be more appropriate. Gilman also discusses the reasons why antihistamine drugs can prevent histamine shock, but usually fail to prevent antigen anaphylaxis.

Epinephrine is the most important sympathomimetic drug and has stood the test of time since its introduction in 1901. All drugs similar to it must be compared with it both as regards efficacy and drawbacks. Much excellent work, especially as regards treatment of asthma, has appeared.

Lowell and Schiller[317,318,444] have three important papers. They first brought on attacks of asthma in three skin-test negative patients by inhalation with extracts of molds, and birch and ragweed pollens, respectively. Tests with four other potent extracts did not cause symptoms. They used a No. 40 De Vilbiss nebulizer with oxygen flowing through aqueous extracts. In four other patients inhalation of all seven extracts were negative, but inhalation of solutions of histamine or acetylcholine produced sharp pulmonary reactions. They then brought on reductions in vital capacity (0-57 per cent) by inhalation of aerosolized extracts of certain pollens and house dust in ten asthmatic patients. Mild asthma usually resulted, though in some trials a fall in vital capacity occurred without signs or symptoms of asthma. Tests with control solutions and control patients were negative. Lastly, an intravenous injection of 0.48 gm. aminophyllin in three asthmatic patients gave the greatest protection against inhalation asthma; epinephrine 0.3-0.5 c.c. (1:1000) gave definite but incomplete protection; atropine and Pyribenzamine (0.6-1.2 mg., intravenously) were totally ineffective. To restore reduced vital capacity resulting from inhalation of pollen extract, the order of effectiveness was: aminophyllin

intravenously, 5 per cent Isuprel by inhalation, and epinephrine subcutaneously. Atropine and Pyribenzamine were again useless. Atropine, however, decreased the response to Mecholyl, and Pyribenzamine protected against and restored vital capacity due to inhalation of histamine; these results suggest that neither acetylcholine nor histamine are determining factors in production of pollen-induced attacks of asthma.

Excellent papers came from France. Hamburger[237] states that an average normal adult exhales about one liter air per second; asthmatics expire 50 to 80 per cent less, not only in the acute stage, but also when the patient seems symptom-free. He found that aminophyllin was the strongest broncho-dilator, acting directly on bronchial muscles. Epinephrine and isopropylepinephrine (Aleudrin or Isuprel) also prevented broncho-constriction (brought on by histamine or acetylcholine). But, on repetition at short intervals, epinephrine loses about 50 per cent of its effectiveness against acetylcholine, thus duplicating epinephrine-fastness as seen in status asthmaticus. The effect of simultaneous use of two broncho-dilating drugs acting by different mechanisms (epinephrine and aminophyllin) is much greater than the sum of the effects of each drug used alone.

Hamburger, Halpern and DeGeorges[240] elaborate on their method of testing the average expiratory rate. They use a spirometer like that for vital capacity, but the patient is told to blow out the air as quickly and completely as he can, and the expiration time is measured with a chronometer. In asthmatics the rate is markedly lowered, usually about 20 to 40 per cent of the normal rate. It usually remains low between spells even when there is no other clinical evidence of asthma. In emphysema and pneumothorax the expiratory rate is normal, even when vital capacity is much reduced. The test, therefore, is simple and clinically valuable.

In support of his paper,[237] Hamburger, Millicz and Halpern[239] connected the trachea of an animal with an apparatus giving a very accurate continuous recording of the bronchial tonus. A constant dose of acetylcholine is injected every third minute, producing each time a sharp and brief increase of bronchial tonus. The animal is then given epinephrine, ephedrine or Aleudrin either intravenously, or by aerosol. At first, the broncho-constricting effect of acetylcholine is completely obviated. Then, as the effect of the sympathomimetic drug wears off, the broncho-constricting effect reappears. Eventually, in 70 per cent of the cases, the constriction caused by acetylcholine becomes greater and may reach a two-fold increase before again decreasing to the same level as before the use of the sympathomimetic drug. This is experimental duplication of epinephrine-fastness observed in status asthmaticus. The authors believe that this phenomenon actually is, in many cases, the direct cause of status asthmaticus. Such a reversed effect is never observed experimentally with aminophyllin and this is in keeping with its excellent clinical results in status asthmaticus. [This work should increase our caution in over-use of epinephrine and similar drugs, especially in status asthmaticus. We, too, have noted much better results in status asthmaticus from aminophyllin than from epinephrine, and have found, as have others, that epinephrine usually regains its value after a few days of avoidance.] In another paper,[238] the same authors give clinical evidence of the effectiveness of aminophyllin and the dangers of increased asthma from an excess of epinephrine, in addition to danger from possible angina, hypertension and possible sudden death. Davy and Thibault[148] studied the action of some new amines which oppose the action of epinephrine on the bronchi.

Castillo and DeBeer[104] sectioned the trachea of guinea pigs into twelve muscular rings of approximately the same widths and tied these rings together to form a chain. The minute changes brought on by bronchoconstrictor and dilator drugs are thereby greatly magnified. The tracheal reactions parallel those of the bronchial muscles in guinea pigs. Epinephrine, aminophyllin and papaverine dilated tracheal muscle, proportional to the dose used. Atropine, Novatropin, Syntropan, Transentin, and Benadryl caused no relaxation and did not relieve spasm induced by barium chloride, but did counteract effects of acetylcholine. In large doses Benadryl contracted tracheal muscle despite the striking antagonism of this drug on histamine-induced contraction.

Isuprel (Aleudrin), now in use for several years, is a better broncho-dilator than epinephrine from which it was manufactured. But it is less efficient in constricting blood vessels and therefore has much less effect against bronchial edema than has epinephrine. Segal and Beakey[452,454] found the drug effective in relieving the dyspnea of bronchial asthma; the lower the vital capacity the greater the degree of relief. Variation in the systolic and diastolic readings in inspiration and expiration were decreased, and undesirable pressor effects and tachycardia were minimal and corresponded to the patient's tolerance to sympathomimetic amines.

The drug should not be given intravenously, nor should more than 0.5 c.c. of the 1:1000 dilution be injected subcutaneously. Sensitive patients should be started on inhalatory doses of 0.5 c.c. of the 1:200 dilution and subcutaneous doses of 0.1 c.c. of the 1:000 dilution, gradually increasing to individual tolerance. Patients in the epinephrine-fast state did well and no fastness to Isuprel was observed. The drug was tried 187 times in eighty-two ambulatory patients by oxygen aerosol and in forty hospitalized patients treated by one or both routes. They also gave tablets of Isuprel to nine patients. It may be good in mild asthma but it is slower in action and, in doses of over 50 mg. causes much nervousness.

Charlier[111] obtained excellent symptomatic relief in 200 patients who had dyspnea from such diseases as bronchial asthma, pulmonary emphysemas of varying degrees, with or without heart failure and cor pulmonale, asthmatic bronchitis and silicosis. A mixture of Aleudrin, Idrianol and novacain was inhaled daily with regular relief of dyspnea. These drugs induce "pneumodilatation," acting synergistically, and in case of circulatory insufficiency they improve cardiac function by increasing oxygenation, cardiac output, and the "analeptic action of Idrianol on the cardiovascular system." Three typical case reports are presented. Such aerosols may also have a prophylactic action, and if used early may prevent the late irreversible effects of silicosis in miners. Charlier,[110] in 197 asthmatic patients, found that if Isuprel is inhaled regularly and in a complete course according to settled rules, excellent results follow in most cases. It is especially good in patients in whom other measures have failed. The article contains an extensive bibliography, diagrams of the apparatus, and tables of results.

Isuprel effectively controls bronchoconstriction and asthma during general anesthesia, say Cohen and Van Bergen.[122] It has little effect on the cardiovascular system, and is non-toxic in therapeutic doses. They recommend 0.5 to 1.0 c.c. of a 1:50,000 solution intravenously during anesthesia, repeated if asthma recurs. They studied seven patients and also noted the bronchodilator and cardiovascular actions of epinephrine, Butanefrin, Benadryl, ephedrine, aminophyllin and Isuprel. Isuprel alone was an effective bronchodilator and yet had little effect on the cardiovascular system. It is particularly indicated in asthmatics who are anesthetized by cyclopropane because this anesthetic may cause some cardiac dysfunction. Siegmund and associates[169] also found Isuprel to be the best bronchodilator in histamine-induced bronchospasm in guinea pigs.

(To be continued in July-August issue, which will include list of references.)

ALLERGENS RESEARCH DIVISION OF THE BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY

On May 15, 1949, the Honor Awards Ceremony of the United States Department of Agriculture was held. On this occasion, the Allergens Research Division of the Bureau of Agricultural and Industrial Chemistry received the following citation:

"For outstanding achievement in fundamental chemical and biological research on the allergenic components of agricultural products, which has markedly advanced scientific knowledge of allergens, made possible more accurate methods for the quantitative determination of allergenic activity, and contributed significantly to wider utilization of farm commodities and to the general health and welfare."

Staff members of this unit are: Henry Stevens, Ph.D., Head; Joseph H. Spies, Ph.D., and E. J. Coulson, Ph.D., Biochemists; Dorris C. Chambers, M.S., Chemist; and Harry S. Bernton, M.D., Clinical Specialist in Allergy and Allergist to Providence Hospital, Washington, D. C.

News Items

FIFTH ANNUAL MEETING—ACA

The Fifth Annual Meeting of The American College of Allergists was held at the Palmer House, Chicago, Illinois, April 14-17, 1949. With a registration of over 1,100, this was the largest meeting devoted to allergy that has ever been held.

The success of the meeting is attributed to the untiring efforts of the Program Committee of which Dr. John H. Mitchell was Chairman, and to the Chairman of the Committee on Local Arrangements, Dr. Leon Unger, and his Host Committee who contributed so generously in making the social activities successful. Also, much credit is due Dr. Jonathan Forman who was in charge of all publicity for the meeting.

There were forty Technical Exhibits and fifteen Scientific Exhibits. The Technical Exhibits represented the leading manufacturers of products related to allergy and included the majority of our Sustaining Members. The Scientific Exhibits represented a wide range of graphic demonstrations pertaining to allergy. Undoubtedly, the attendance was greatly augmented by the excellent Technical and Scientific Exhibit.

The program ranged from the fundamental investigations of immunology and allergy to practical clinical investigations, new drugs used in allergy, the psychosomatic factors of allergy, a symposium on cottonseed oil sensitivity and a panel discussion on pediatric allergy.

The Local Committee on Arrangements and the Host Committee composed of members in Illinois and adjacent states, arranged for the luncheon and style show at Marshall Fields, as well as the Breakfast Club Broadcast, for the ladies.

The annual banquet held on Saturday evening, April 16, was well attended. Short talks were presented by the retiring president, George E. Rockwell and the incoming president, Jonathan Forman. The wine for the banquet was generously supplied by Marcelle Cosmetics, Inc., Chicago, Illinois.

Business Meetings

At the business meeting of the Board of Regents, it was decided that the next annual meeting of the College would be held in St. Louis, Missouri. Since then definite arrangements have been made to hold the sixth annual meeting at the Hotel Jefferson, St. Louis, Missouri, January 15-18, 1950. Registration for this meeting will commence at 2 p.m., Sunday, January 15, but there will be no Technical or Scientific Exhibits on Sunday. Monday, Tuesday and Wednesday will be devoted to a Scientific Program, as well as a Technical and Scientific Exhibit.

The Board of Regents voted fourteen members to Active Fellowship at this meeting. During the past year a total of thirty-one members have been voted to Active Fellowship. This list includes: Albert Avedon, M.D., William Harvey Blank, M.D., Sidney H. Carsley, M.D., Pasquale Cioffi, M.D., James F. Claney, M.D., James E. Culleton, M.D., Ross Dale Dickson, M.D., Erna S. Enderle, M.D., Seymour Fisher, M.D., Arthur A. Goldfarb, M.D., Benjamin F. Gordon, M.D., Dorenee O. Hankinson, M.D., Herman A. Heise, M.D., Preston S. Herring, M.D., Harry H. Hershey, M.D., Leo Hoehfeld, M.D., Stanislaus H. Jaros, M.D., A. Paul Knott, M.D., Herman M. Lubenstein, M.D., Eugene J. Luippold, M.D., B. Thomas McMahon, M.D., Joseph P. Maher, M.D., Roy R. Matteri, M.D., William L. Mermis, M.D., Ira R. Morrison, M.D., Anthony F. Piraino, M.D., Raymond S. Rosedale, M.D., Alvin Slipyan, M.D., George Knox Spearman, M.D., Gardiner S. Stout, M.D., and Harry R. Weil, M.D.

During the past year the College has been unfortunate in the loss, through death, of the following: George C. Anglin, M.D., Active; Vincent J. Irwin, Jr., M.D., Active; Voyle M. James, M.D., Active; Philip J. Jordan, M.D., Active; William A. Mowry, M.D., Active; Herman Spitz, M.D., Active; and Clarence K. Weil, M.D.,

Active. Obituaries have appeared in the ANNALS OF ALLERGY, and condolences have been sent to the families.

At the general business meeting of the College on Saturday, April 16, the following members were elected to serve the ensuing year:

President-Elect—Dr. John H. Mitchell
First Vice President—Dr. Homer E. Prince
Second Vice President—Dr. John P. Henry
Secretary-Treasurer—Dr. F. W. Wittich
Board of Regents (one-year term)—Dr. Herbert J. Rinkel

A detailed report of the College finances was presented by Dr. Hal M. Davison, Chairman of the Finance Committee. The report was approved as read. The report reads as follows:

Physical Setup of The American College of Allergists, Inc.

We have investigated the space used by The American College of Allergists and our opinion is that as little space as can be used is being used and that this is paid for at the current rate in the city. The space used by The International Association of Allergists is separate from the College. The American College of Allergists does not furnish an office personally for Doctor Wittich or Mrs. Wittich.

The necessary furniture, equipment and supplies used by the College are owned and used by the College.

The salaries of the employes have been broken down and placed in the proper accounts. The one stenographer used by Doctor Wittich personally is paid for by the hour by Doctor Wittich. Any stenographic work for The International Association of Allergists is also paid for by the hour by The International Association of Allergists. Stenographic work for the Quarterly Review of Allergy and Applied Immunology has been computed on an average and is paid for on a monthly basis.

All checks are countersigned by the Assistant Treasurer, Doctor Albert V. Stoesser.

Travel Allowance

The report of the auditor on travel allowance has been broken down with the representative of the auditing company present and it has been analyzed to the last penny. It is agreed by the committee that Doctor Wittich's expenses should be paid to any meeting where he actually represents the College and for the duration of time that he is on College business. These expenses should include car fare, hotel bills, meals and incidental expenses.

Entertainment

It is recognized by the Finance Committee that a certain amount of entertainment of the proper people should be done by The American College of Allergists, but this should be exceedingly limited and should not include officers, the Board of Regents, Fellows, members or employes of the College who may be visiting Minneapolis or present at any of the meetings. We do not feel that set rules may be laid down for this entertainment, but that this must be left to the discretion of the Secretary, himself, when in his opinion it would be for the actual good of the College. It is recommended that the bill for entertainment should not exceed for one year, under any circumstances, $250.00.

It is also recognized by the Finance Committee that Doctor and Mrs. Wittich cannot personally afford to entertain visitors to the home office of The American College of Allergists, nor can the College, and this should neither be expected or accepted, if offered.

Annual Audit

It is requested by the Finance Committee that there be an annual audit of the books and that this include an itemized breakdown of the expenses of the annual meeting, in-

structional courses, travel expenses and entertainment, in addition to those items already broken down.

It is also requested that at this annual audit, the auditor examine the methods of running the office as to its efficiency and that recommendations be made for changes necessary for increased efficiency and economy and that a report of this be included in the audit.

Recommendations

It is recommended to the Board of Regents that:

1. The sale of the 1948 Instructional Courses be put on sale for $5.00 and that the older copies be put on sale for $2.50.
2. A registration fee of $5.00 be made for all non-members at the annual meetings.
3. The printing of instructional courses be discontinued and that, instead, they be mimeographed, with no cuts.

Proposed Budget

The Finance Committee has considered the expense of running the office and recommend the following budget for the ensuing year:

Sinking Fund	$1,706.00
Bruce Publishing Company ($6.00 for each member for ANNALS OF ALLERGY)	5,118.00
Bruce Publishing Company (Progress notes, Bound Volumes)	500.00
Certificate Printing	200.00
Salaries:	
1 girl, $2,500 a year	2,500.00
4 girls, $2,400 a year (including Mrs. Wittich)	9,600.00
Dr. F. W. Wittich	1,200.00
Office Supplies and Expense	500.00
Postage	500.00
Rent	1,300.00
Electricity	324.00
Telephone and Telegraph	500.00
Audit and Legal Fees	300.00
Entertainment	250.00
Travel	600.00
Petty Cash (for miscellaneous items too small for checks)	300.00
	$25,398.00

After checking the budget, it is anticipated that further revenues will be made by selling past instructional courses, new members and Fellows, advance of members to Fellowship, more Sustaining Members and the decrease in cost of the instructional courses by mimeographing the outlines instead of printing them.

Our President, Dr. George E. Rockwell, and the Finance Committee as a whole visited Minneapolis for two days and have personally checked the items mentioned above in the presence of a representative of the firm of auditors. The auditor assured the Finance Committee that every check and every voucher for petty cash had been verified and was included in the audit. The expenses of Doctor Rockwell and the Finance Committee for this trip cost the College nothing.

HAL M. DAVISON, M.D., *Chairman*
ALBERT V. STOESSER, M.D., *Assistant Treasurer*
HARRY L. ROGERS, M.D.
BOEN SWINNY, M.D.
F. W. WITTICH, M.D.

A Financial Report of the ANNALS OF ALLERGY was read by the Secretary and accepted.

The following resolutions were adopted by the Board of Directors, the Board of Regents and the College-at-Large:

Resolutions

I. WHEREAS, in many societies there is a tendency over the years to concentrate the administration of the Society in the hands of a few men,
WHEREAS, this practice arises in most instances through the practice of advancing an officer through a succession of positions until finally after seven or eight years he rises more or less automatically to presidency,
WHEREAS, this practice is in the opinion of the Board of Directors a critical mistake in policy in that it only allows about fifty men to serve the Society in fifty years, and thus deprives the Society of the help of many men of ability, and,
WHEREAS, the Board of Directors would regret to see this practice established in our College,
THEREFORE, BE IT RESOLVED that it is the sense of the Board of Directors and it so recommends to the Board of Regents that:
1. No one who has in the past held an elective office in the College should be nominated for another such office, except that all past officers other than past-president, are eligible at any time for consideration in selecting nominations for the presidency—nor does this apply to the office of secretary-treasurer;
2. Physicians recently elevated to or elected to Fellowship in the College should not be considered for an elective office in the College until after a reasonable number of years have elapsed in which such a Fellow may have time to demonstrate his loyalty and ability to the College;
3. A policy be inaugurated, as far as practicable, to spread the offices of the College as widely as possible on a geographical basis;
4. Furthermore, if this program be adopted, it is recommended by the Board of Directors that it be published in the ANNALS OF ALLERGY and that each year the Secretary of the College shall give a copy of these resolutions to each member of the Nominating Committee for his guidance.

II. WHEREAS, from time to time the temptation arises to place past-presidents back on the Board of Regents and thus to limit the number of men who can throughout the years hold office,
THEREFORE, BE IT RESOLVED that it is the sense of the Board of Directors that the By-Laws of the College be changed so that all past-presidents of the College have the right to attend all meetings of the Board of Regents and the privilege of the floor for the purpose of discussion, but no such past-president shall have a vote in the deliberation of the Board of Regents.

Congratulatory cablegrams were read from Dr. Paul Kallós of Sweden and Professor Jimenez Diaz of Madrid, Spain, President of the Spanish Allergy Society. Personal greetings were extended by Doctor Estrada de la Riva, President of the Cuban Allergy Society.

The business meeting adjourned with the introduction of the new president, Dr. Jonathan Forman.

THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

Final arrangements are now being made by Professors A. Grumbach and C. W. Loffler to hold the First International Congress in Allergy of the International Association of Allergists in Zurich in the early fall of 1951. Because of the large number of international congresses which are scheduled for 1949 and 1950, it was decided to postpone the Congress in Allergy until 1951.

The first issue of the *International Archives of Allergy and Applied Immunology*, the official publication of the International Association, is now in press. This is being published by S. Karger, Ltd., Publishers, Basel, Switzerland, and the distributor in this country is Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, New York. The subscription price of $10 per year is included in the annual dues of those members of the IAA who have been able to pay their full dues. All members of the International Association, both Individual Members and Members of any society belonging to the IAA, are invited to submit manuscripts to the Editorial Board for its approval for publication in the new *International Archives*. These may be published in the native language of the various countries. All the allergy societies, which are members of the IAA, have been cordially invited to print their proceedings in the *International Archives*.

Fourteen of the twenty-three existing allergy societies in the world at the present time are official members of the International Association of Allergists. The British Association of Allergists, of which Dr. Vera B. Walker is President of the Council, has just recently applied to the International Association for affiliation and has been accepted as a society member.

Active Fellows of the American College of Allergists who are interested in joining the IAA as Individual Members should write for information to the Chairman of the Executive Committee, 424 La Salle Medical Building, Minneapolis 2, Minnesota.

1949 FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

The 1949 Fall Graduate Instructional Course in Allergy of The American College of Allergists will be conducted under the auspices of Baylor University School of Medicine, Houston, Texas, October 31 through November 5. This will be a five and one-half day course. Instructors of outstanding ability are already being selected for the faculty. The diagnosis and treatment of allergic diseases, as well as the basic sciences pertaining to allergy, will be presented. Round table discussions will occupy two evenings.

Both members and non-members are cordially invited to attend. The headquarters will be at the beautiful Shamrock Hotel. The price for this course will be $100.00. For reservations write to Mrs. Ellsworth, Shamrock Hotel, Houston, Texas.

CIVILIAN DOCTORS SOUGHT FOR PANAMA CANAL ZONE

Permanent appointments for physicians in the Civil Service now exist in the Panama Canal Medical Service according to an announcement from the Office of The Panama Canal, Washington, D.C.

Starting professional salaries are $5,599 and $6,540 a year, with free transportation to the Canal Zone provided for physicians, their families and household goods. In addition, doctors who receive appointments get two months' paid vacation (including time lost by illness) and reduced fares on Panama Line passenger vessels.

Physicians who are interested in a position as medical officer in the Panama Canal Zone should address their applications to Chief of Office, The Panama Canal, Washington 25, D. C.

DEPARTMENT OF CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

Dr. L. O. Dutton of El Paso, Texas, who has charge of the Department of Clinical Pathology and Laboratory Procedures, in the ANNALS, is very desirous of having members of the College send in material for this department. If you have a new laboratory procedure which applies to allergy or clinical pathology, Doctor Dutton and the members of the Editorial Board will greatly appreciate your submitting the procedure directly to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas, for editing. In the past, suggestions from this department have been very valuable, and it is hoped that interest will continue.

CALIFORNIA SOCIETY OF ALLERGY

A successful meeting of the Allergy Section of the California Medical Association and the California Society of Allergy was held May 8 and 9 at the Biltmore Hotel, Los Angeles, California. On May 8 there was a joint meeting of Allergy, General Medicine and General Practice Sections. The Allergy Section Meeting of the California Society of Allergy was held on May 9 followed by a dinner meeting that evening.

NEWS ITEMS

CONNECTICUT ALLERGY SOCIETY

The second annual meeting of the Connecticut Allergy Society was held on May 4, 1949, in New Britain, Connecticut, in conjunction with the annual meeting of the Connecticut State Medical Society. Doctor Matthew Walzer of Brooklyn, New York, spoke on "Management of Bronchial Asthma". It was a very stimulating and instructive paper and brought forth considerable discussion. The meeting was extremely well attended by members of the Society and guests.

A business meeting preceded the clinical session at which time the election of officers took place. Sidney W. Jennes, Waterbury, was re-elected President, Barnett Freedman, New Haven, Vice-President, Russell Webber, Waterbury, Secretary-Treasurer, and Arthur Roche and Vincent Cenci, Hartford, members of the Executive Committee.

ISRAEL SOCIETY OF ALLERGY

The Israel Society of Allergy has been founded and is now limited to Jerusalem but later on will be extended to all of Israel. Officers of the Society are: President, Dr. M. J. Gutmann; Prof. B. Zondek; Prof. G. Witenberg, and Doctor Tass.

LOUISIANA ALLERGY SOCIETY

At the recent meeting of the Louisiana Allergy Society the following program was presented: "The Injudicious Use of Intranasal Medication" by Dr. A. J. McComiskey of New Orleans; "Khellin" by Dr. Vincent J. Derbes of New Orleans; "Orthoxine in Bronchial Asthma" by Drs. Henry D. Ogden and Louis Cullick, both of New Orleans; and "Asthma in Childhood" by Dr. J. Dudley Youman, Jr., of Shreveport. Dr. Henry D. Ogden of New Orleans presided over this meeting.

The following officers were elected: President, Dr. J. Dudley Youman, Jr.; Vice President, Dr. H. Whitney Boggs, and Secretary, Dr. Vincent J. Derbes.

MEXICAN SOCIETY OF ALLERGISTS

The Directive Council of the Mexican Society of Allergists was changed January 29, 1949, and the following members have been elected: President, Dr. Carlos Canseco; Vice President, Dr. M. Salazar Mallen; Secretary, Dr. Julio V. Cueva; Treasurer, Dr. Oscar de la Fuente.

THE NEW JERSEY ALLERGY SOCIETY

Dr. Nathan Schaffer, President of the New Jersey Allergy Society, has made the following announcement.

The New Jersey Allergy Society has formed a Committee on Aerobiology to do an air survey of the state of New Jersey for the purpose of finding allergenic factors not presently recognized. The work will be done in the following fields: Pollen surveys, Bacteria surveys, Fungi surveys, Chemical contaminants, and Meteorology.

With funds supplied by Schering Laboratories, six Wells Air Centrifuges will be set up in widely separated sites in the state. Daily air specimens will be studied. The chairmen for the entire project are Nathan Schaffer, M.D., of East Orange, New Jersey, and Edward E. Seidman, M.D., of Plainfield, New Jersey. Sub-Chairmen are as follows: **Pollen**, L. Byck, M.D., Newark; **Bacteria**, E. Seidman, M.D., Plainfield; **Fungi**, N. Schaffer, M.D., East Orange; **Chemical contaminants**, C. Weston, M.D., Glen Ridge; and **Meteorology**, F. Rosen, M.D., Newark.

The sub-committee on Mycology, which consists of Doctors Schaffer, Seidman, Byck, Suesserman, and Feldman, are attending conferences on Mycology four hours a week at Rutgers University in New Brunswick, under the direction of C. M. Haen-

seler, M.D., and B. H. Davis, M.D., of the Department of Plant Pathology, College of Agriculture. These conferences started with the school term in February, and plans are being made for their indefinite continuance. Doctors Haenseler and Davis will work with this committee in attempting to identify any fungi found in quantity. Extracts of these will be made and sent to all members of the Society for clinical testing and evaluation.

Plans are being made to set up similar conferences in Bacteriology and Pollen identification at Rutgers in the near future.

THE NEW YORK ALLERGY SOCIETY

The following have been elected as officers of the New York Allergy Society: President, Max Grolnick, M.D.; President-Elect, James Barnard, M.D.; Vice-President, Matthew Brunner, M.D.; Secretary, Frederick Brown, M.D.; and Treasurer, Paul de Gara, M.D.

Dr. Jack A. Rudolph of Miami Beach, Florida, has retired from private practice and has accepted a position as senior grade physician, consultant in Internal Medicine and Allergy, with the Veterans Administration. His new address is Veteran Administration, 3300 N.E. Second Avenue, Miami, Florida.

Dr. Alfred J. Weil has announced the opening of his office for the practice of clinical allergy at 106 Franklin Avenue, Pearl River, New York.

CHILEAN ALLERGY SOCIETY

The First Congress of the Chilean Allergy Society was held on January 3 to 6, 1949, at Santiago. Dr. Edo. Diaz Carrasco is President of the Society and Dr. Ricardo Guzman is the Secretary. There was a reception for the Honorary Members of the Society at the session on the first day of the Congress, and the following papers were presented: (1) "Allergy in Clinical Practice" by President Edo. Diaz Carrasco and Prof. Hernan Alessandri, and "Antihistaminics" by the Secretary, Dr. Ricardo Guzman; (2) "Our Experience with Ten Cases of Asthma" by Drs. Migual Hermosilla, Zoltan Bernath and Humberto Richetti; and (3) "A Study of Severe Asthma." "Methods of Practical Therapeutics." "The Use of the Bronchoscope." "The Relation of Allergic Flora in Brazil." Presented by Dr. Jorge Anwandter in the absence of the authors, Drs. Paulo Dias da Costa, J. C. Guimeraes and Th. Vian.

On January 4 the following papers were presented: (1) "The Pathology of the Anatomy of Allergy" by Dr. Hector Rodriguez; (2) "Allergenic Flora of Chile" by Dr. Sr. Juan Ibanez and Dr. Zoltan Bernath; and (3) "Allergy from Molds," presented by Dr. Hugo Donoso and Prof. Hernan Alessandri in the absence of Dr. Fred W. Wittich.

On January 5 the following papers were presented: (1) "Dermatologic Allergy" by Dr. Arturo Mardones; (2) "The Allergy Specialist and the Plant Sensitivity of Chile" by Drs. Alejandro Reyes and Humberto Richetti; (3) "Endocrine Factors in Allergy" by Dr. Rafael Tellez; and (4) "Treatment with Tuberculin and Some Affections Considered Allergy" by Dr. Jorge Anwandter.

This First Congress was well attended and its officers and Program Committee are to be congratulated for its success.

SPANISH ALLERGY SOCIETY

The Spanish Allergy Society has just held its First National Congress in Allergy at Madrid, May 26, 27, and 28, 1949. Prof. Jimenez Diaz, President of the Society, held a reception welcoming the guests on the evening of May 25 at the Hotel Ritz.

On the morning of May 26 Prof. Jimenez Diaz and Drs. C. Lahoz Marques and F. Lahoz presented a paper on the "Concept, Definition, and Classification of Bronchial Asthma in Spain." The remainder of the day was devoted to a symposium on the subject.

On May 27 there was a lecture on "Allergic Dermatologic Diseases" presented by Profs. Gay Prieto, Gomez Orbanejz and Vilanova, followed by a symposium.

On May 28 Drs. Arjona Trigueros and Ales Reinlein presented a paper on "Anaphylaxis and Allergy. Its Mechanism and Significance" which was followed by a discussion. At the afternoon session there were three discussions of the entire program, which were followed by a dinner at the Hotel Ritz closing the meeting of the First National Congress in Allergy.

AIR FORCE MEDICAL RESERVE IS ESTABLISHED

General Hoyt S. Vandenberg, Chief of Staff, U. S. Air Force, announced today that applications are being received for commissions in the newly created Air Force Medical Reserve. Physicians, dentists, nurses, and other medical personnel who served with the Army Air Forces during the war may make application through the Air Adjutant General, U. S. Air Force, in Washington.

THE QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

A notice is hereby given to all subscribers to the *Quarterly Review of Allergy and Applied Immunology* that this publication will be under new management beginning with the June issue. Owing to the many details necessary for this transaction, the June issue will probably not appear until the latter part of July. The new *Quarterly* will be published by the Bruce Publishing Company, publishers of the ANNALS OF ALLERGY. A special combination rate will be available to subscribers to ANNALS OF ALLERGY. The *Quarterly* will be greatly enlarged and will include many more reviews than heretofore. The Editorial Staff is being reorganized, and the names of many notable physicians will be added. The style and format of the *Quarterly* is being completely revised. The reviews will be concise, critical accounts of the publications and will embrace the essential literature on allergy and immunology throughout the world.

REDUCED PRICE FOR INSTRUCTIONAL COURSES

These comprehensive abstracts of postgraduate instructional courses held under the auspices of the various universities by authorities on the subject are now on sale at a greatly reduced price. The 1948 lecture courses held under the auspices of the University of Oregon Medical School at Portland, Oregon, will be sold for $5 a complete set. All other previous courses are now on sale at $2.50 a set. Mail your orders to The American College of Allergists, 423 La Salle Medical Building, Minneapolis 2, Minnesota.

IN MEMORIAM

HERMAN SPITZ, M.D., F.A.C.A.

We sincerely regret to announce the death of Dr. Herman Spitz of Nashville, Tennessee, on February 4, 1949. His death was due to heart complications.

Doctor Spitz was born June 29, 1885, in Hungary and received his medical education at Vanderbilt University, graduating from that institution in 1912. Postgraduate work was done at Cornell University and Harvard. For a time he taught at Vanderbilt University. He was a member of the hospital staffs of Woman's Hospital, Baptist Hospital, St. Thomas Hospital and General Hospital of Nashville. Doctor Spitz was a member of the American Medical Association, the American Society of Clinical Pathologists and a Fellow of the American College of Allergists.

Doctor Spitz is survived by his wife, Helene, and one daughter, Mrs. Ruth S. Beck. The members of the College extend their sincere sympathy to the family.

THE TREATMENT OF BRONCHIAL ASTHMA WITH ISUPREL

(Continued from Page 389)

relieved the so-called epinephrine-resistant types of dyspnea. Its side reactions were not as severe as the side reactions of epinephrine.

3. Isuprel orally was the least efficient of this group in the treatment of bronchial asthma.

4. Side reactions so common with this group of Isuprels were not comparatively greater than the side reactions occurring after the use of such other drugs as ephedrine, aminophylline, and epinephrine.

REFERENCES

1. Dautrebande, L.; Philippot, E.; Charlier, R., Dumoulin, E.: Medicamentous aerosols. Treatment of asthmatiform states with aerosols, pneumodilatory substances and autogeneous vaccines. Presse med., 50:566, 1942.
2. Konzett, H.: Neues zur Asthma Therapie. Klin. Wchnscher., 19:1303-1306, (Dec. 21) 1940.
3. Rössler, R.: Neue Wege der Asthmatherapie. Wien. klin. Wchnschr., 53:974-975, (Nov. 22) 1940.
4. Segal, M. S., and Ryder, C. M.: Penicillin aerosolization in the treatment of serious respiratory infections. A preliminary report. New England J. Med., 233:747, (Dec. 20) 1945.
5. Segal, M. S.: Inhalational therapy in respiratory disease. Bull. New England M. Center, 5:104-108, 1943.
6. Segal, M. S., and Beakey, J. F.: Bull. New England M. Center, 9:62-67, (April) 1947.
7. Segal, M. S., and Beakey, J. F.: Ann. Allergy, 5:317-336, (July-August) 1947.
8. Segal, M. S.: Inhalational therapy. New England J. Med., 230:456-465 and 485-493, 1944.
9. Stolzenberger Seidel, M.: Klinische Untersuchungen zur Behandlung des Asthma Bronchiale. Klin. Wchnschr., 19:1306-1310, (Dec. 21) 1940.

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BOOK REVIEWS

TECHNIQUES of HISTO- and CYTO-CHEMISTRY. By David Glick. Pages XXIV plus 531. Price $8 00. New York: Interscience Publishers. 1949.

Dr. R. R. Bensley, who has himself done so much to forward our knowledge of the chemistry of the cell, has written an appreciative foreward to this useful compendium. And compendium it is, for Dr. Glick has assembled a veritable storehouse of apparatus and procedures.

Few books, Lee's *Microtomists Vade Medum* excepted, offer so much help to the reader by assembling all the known methods for a preparation and explicitly giving "cook-book" directions for each. The microscopic or on-the-slide methods of chemical analysis are given in the first section. These are followed by a fully detailed section on the fairyland of microchemistry. Grams become micrograms, burettes become capillary tubes controlled by micrometers, and we are introduced to the fantastic accuracy of the Cartesian diver. Lilliput indeed! A one-entry section on microbiological assay follows to be succeeded by twenty-eight pages devoted to the use of various high-speed centrifuge techniques to biological analysis. Throughout the book are neat and instructive diagrams of apparatus. An extensive bibliography and an index complete the volume, to which has been thoughtfully added a list of manufacturers.

The book is a "must" for all chemically minded microscopists and biological chemists. Treating as it does, a labile and progressing field, we may expect that the author—now on a technique collecting expedition to Scandinavia—will revise the work at frequent intervals. To make it subject to as frequent revision as will be necessary and still find adequate sales, the publishers will probably have to consider a less expensive format, for the book seems somewhat over-priced.

BERRY CAMPBELL, Ph.D.
University of Minnesota

EXPERIMENTAL IMMUNOCHEMISTRY. By Elvin A. Kabat, Ph.D., Associate Professor, College of Physicians and Surgeons, Columbia University, New York, and Manfred M. Mayer, Ph.D., Associate Professor, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. 567 pages, 88 figures. Springfield, Ill.: Ch.C., Thomas, 1948.

The term "immunochemistry" has become established for the application of exact methods of chemistry and physics in immunology. One may perhaps regret the psychological barrier thus created between a "high brow" and a "low brow" type of immunology. But there is no denying that the men who made the word immunochemistry a badge of academic distinction have made an immense contribution to the revival of immunology during the last twenty years. Their beneficial influence upon the thinking and the techniques of those who may be called the craftsmen of immunology—including the physicians practicing allergy—will be further extended by the present volume. It gives a comprehensive picture of the techniques which have proven so fruitful in the investigation of immunological phenomena.

To those conversant with the immunochemical work of recent years, the names of the two authors are familiar as very active participants in the investigational work in Dr. Heidelberger's laboratory and, more recently, for outstanding work in their own establishments. Their extensive experience is mirrored in detailed and critical descriptions of methods and discussions of their aims, achievements and limitations, which will offer to the beginner as good an initiation as the printed word can convey. The experienced will read the book with pleasure and profit for the sake of

critical appraisal and sound practical advice, not to mention the convenience of having a wealth of data at hand instead of having to unbury them from the library shelves. Access to the original descriptions and to more extensive discussions of the subjects is facilitated by a well-selected bibliography.

The scope of the book is best described by a short review of its table of contents: Part I covers general immunological methods like precipitation, complement fixation, and tests for supersensitivity. Part II treats the applications of quantitative methods, as the estimation of antigens and antibodies, criteria of homogeneity, cross reactions. Part III describes in twenty-three chapters chemical and physical methods, including ultracentrifuge, electrophoresis, and diffusion. There follows in Part IV the techniques of preparing typical compounds, as used in the work of Heidelberger and others, such as crystalline proteins, protein derivatives, microbial carbohydrates, and purified antibody solutions. A concluding section contains a miscellany of data, as on the cleaning and calibration of glassware and animal techniques.

It is hoped that this book will not only find its way to the book shelves of laboratories concerned with investigative and experimental allergy, but that it will also be studiously consulted. It will prove to be a reliable and stimulating friend.

A.J.W.

THE 1948 YEAR BOOK OF EYE, EAR, NOSE AND THROAT. By Louis Bothman, M.D., and Samuel J. Crowe, M.D., with the collaboration of Elmer W. Hagens, M.D. 511 pages. 100 figures. Price $4.75. Chicago: The Year Book Publishers, 1948.

Many new diagnostic and therapeutic procedures applicable to the type of cases seen frequently in practice are offered in this latest volume.

As formerly, there are three parts: (1) the eye; (2) the ear; and (3) the nose and throat. The first chapter contains seventeen articles dealing with all diseases involving the eye, and there are ten articles covering diseases of the ear, nose, and throat.

The Year Book Quiz, consisting of twenty questions, is looked forward to each year since it is a test of one's familiarity with the current literature.

Of particular interest to the allergist is the information that large doses of Vitamin A have a specific therapeutic effect in solar retinitis and that eosinophiles do not occur in a normal conjunctiva, whether there is eosinophilia of the blood or not. The diseased conjunctiva presents eosinophilia in a number of conditions, the commonest of which are typical and abortive vernal conjunctivitis and allergic conjunctivitis. The editors, however, point out that it is much easier to find eosinophiles in the nasal secretions of these patients, and they believe that simple allergic conjunctivitis, abortive vernal catarrh and typical vernal conjunctivitis are of the same origin and vary only in intensity and duration. Molds are incriminated as an etiologic agent even in the "cobblestone" type of vernal catarrh. Allergic manifestations were found (Kjaer-Copenhagen) in 25 per cent of cases of Ménière's disease.

The illustrations, print, and paper stock are excellent.

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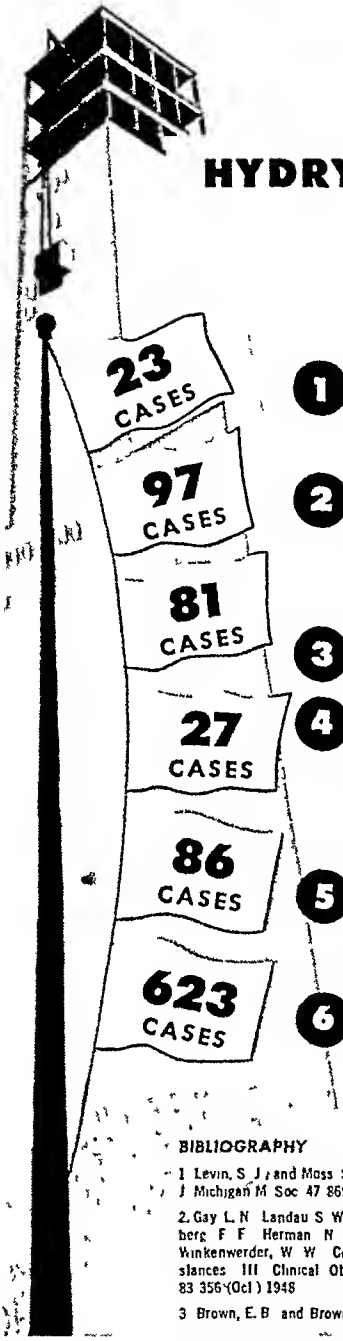

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"% benefited . . . 73"[2]
"relief obtained"[3]
"definite relief"[4]
"relieved 56 per cent"[5]

1 "The results in hay fever with Hydryllin were very striking. Twenty of twenty-three seasonal hay fever patients (86.9 per cent) were markedly benefited, receiving relief varying from 50 to 100 per cent."[1]

2 "% benefited . . . 73."[2] In table 1 it is shown that Hydryllin benefited 73 per cent of ninety-seven patients with seasonal and perennial allergic rhinitis.

3

"Symptom	Number of patients	Relief Obtained 100%	75%	50%	20%	0
Hay Fever	81	39	12	11	5	14"[3]

4 ". . . in a group of hay fever cases, 14, or 52 per cent, obtained definite relief (50 to 100 per cent amelioration of symptoms) with Hydryllin. In some cases relief followed immediately after the first use of the drug, but in other cases it was necessary to increase the dose to three to six tablets daily."[4]

5 "Hydryllin relieved 56 per cent of 86 patients. . . ."[5]

AND IN ASTHMA

6 "In the asthmatic cases, both those with asthma due to pollen and those having asthma from other sources, the figures of the effectiveness of the drug are more impressive than those of other antihistaminics."[6]

BIBLIOGRAPHY

1 Levin, S J, and Moss S S Hydryllin in Asthma and Hay Fever, J Michigan M Soc 47 869 (Aug) 1948

2. Gay L N Landau S W Carliner, P E Davidson N S Fursten berg F F Herman N B Nelson W H Parsons, J W, and Winkenwerder, W W Comparative Study of Antihistamine Sub stances III Clinical Observations, Bull Johns Hopkins Hosp 83 356 (Oct) 1948

3 Brown, E. B and Brown F W. The Use of a New Antihistaminic Combination in the Treatment of Allergic Disorders New York State J Med 48 1465 (July 1) 1948

4 Markow, H, Bloom S and Leibowitz H · An Evaluation of Hydryllin (Diphenhydramine and Aminophyllin) in the Symptomatic Treatment of Allergy, New York State J Med 48 2390 (Nov 1) 1948

5 Arbesman, C E Comparative Studies of Several Antihistaminic Drugs, J Allergy, 19 178 (May) 1948

6 Committee on Therapy of the American Academy of Allergy, St Louis Dec 15 17, 1947

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1. Horton, B.T., Ryan, R. E. & Reynolds, J. L., Proc. Staff Meet. Mayo Clinic, 23:105, Mar. 3, 1948.
2. Friedman, A. P., N. Y. State Jl. of Med. (in press).
3. Ryan, R. E., Postgraduate Medicine (in press).
4. Hansel, F. K., Annals of Allergy (in press).

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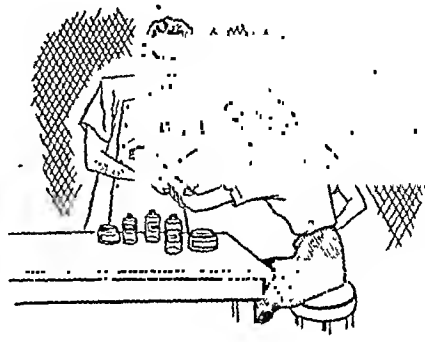

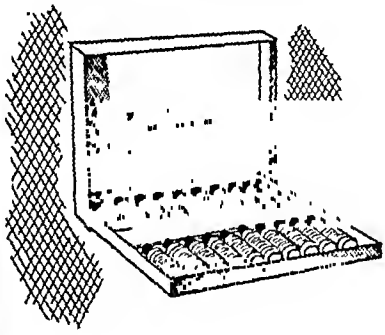

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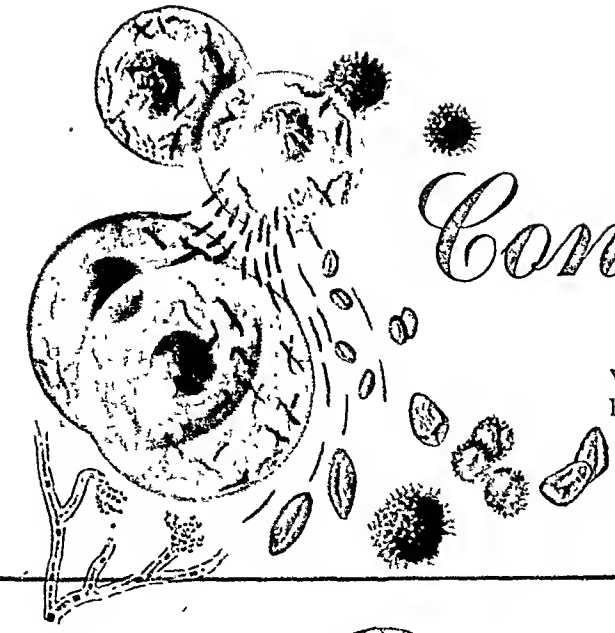

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with an allergen and subsequent release of histamine is considered to be the mechanism of allergic disorders.

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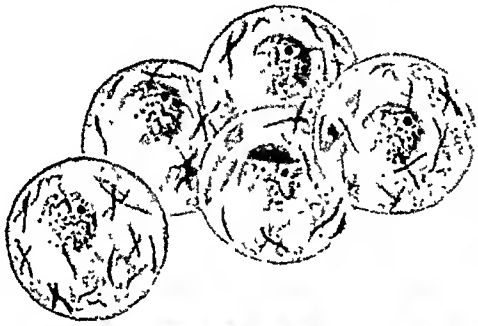

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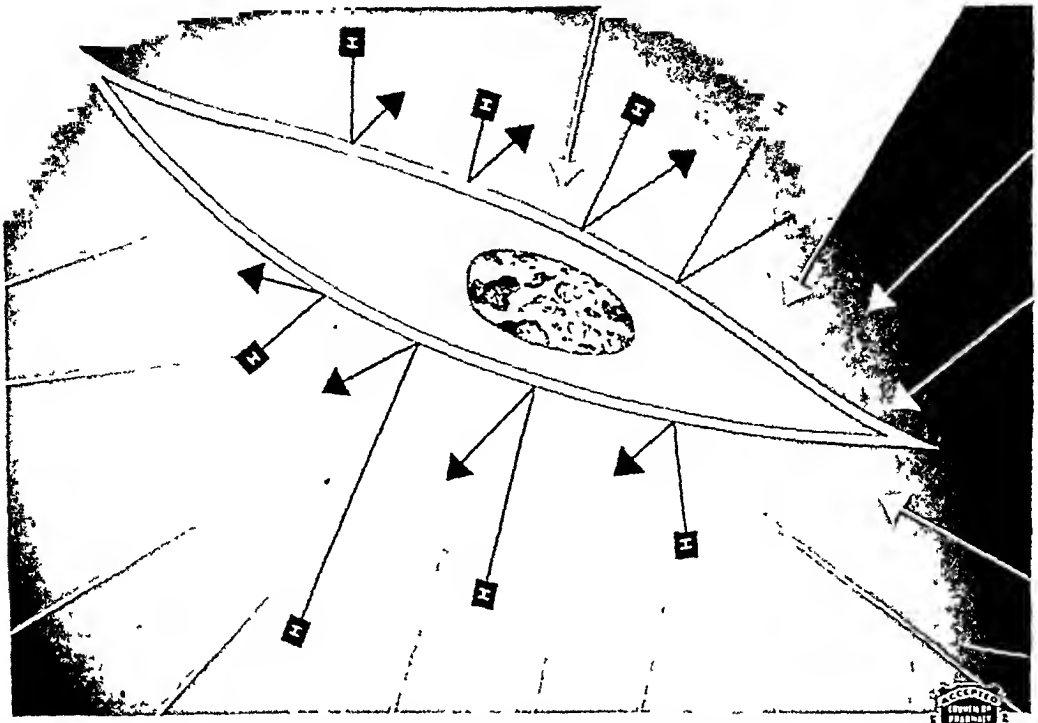

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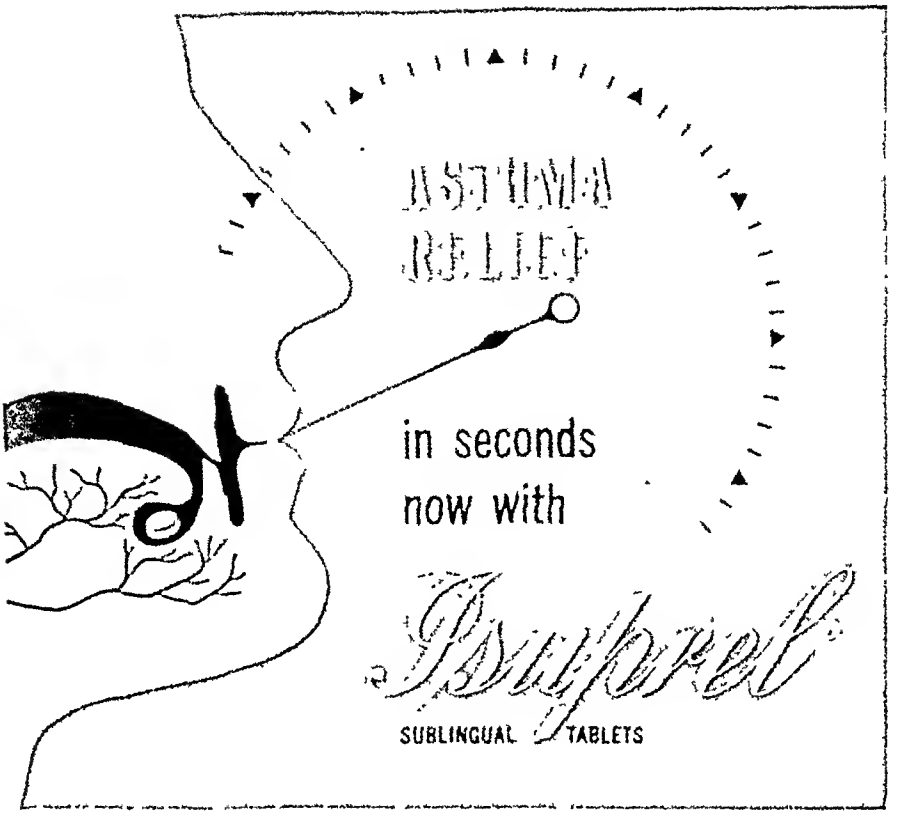

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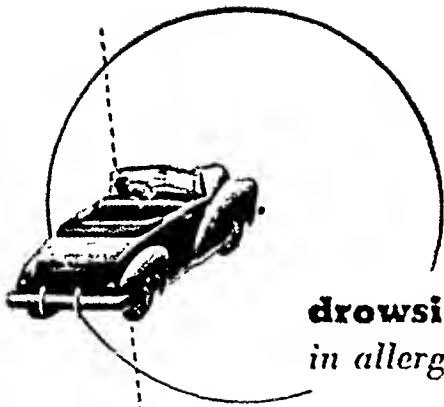

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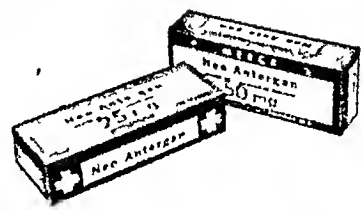

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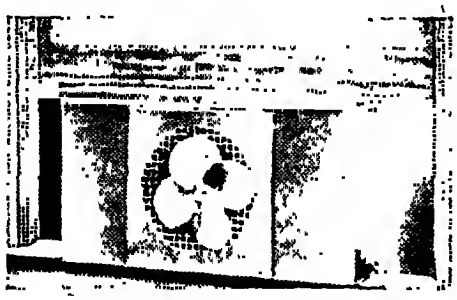

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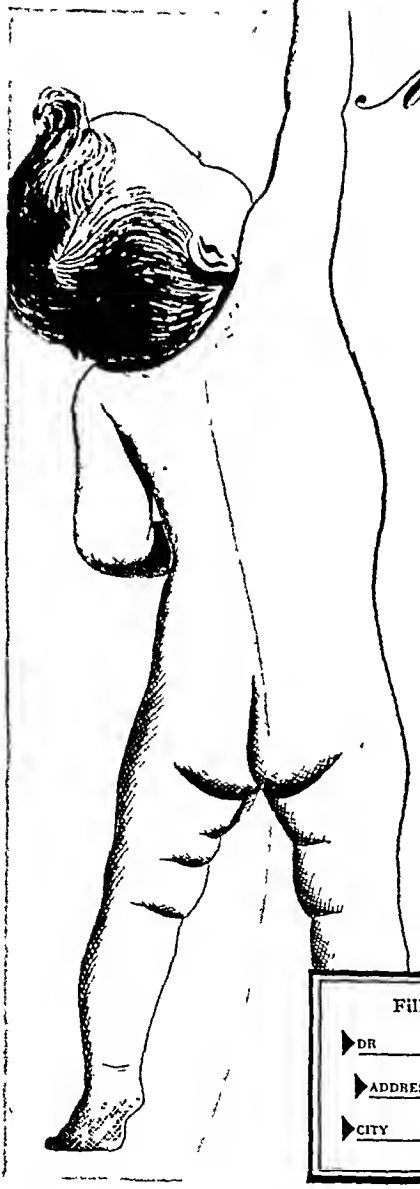
In
infant allergy to
cow's milk lactalbumin



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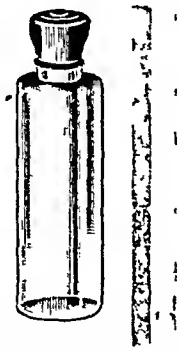

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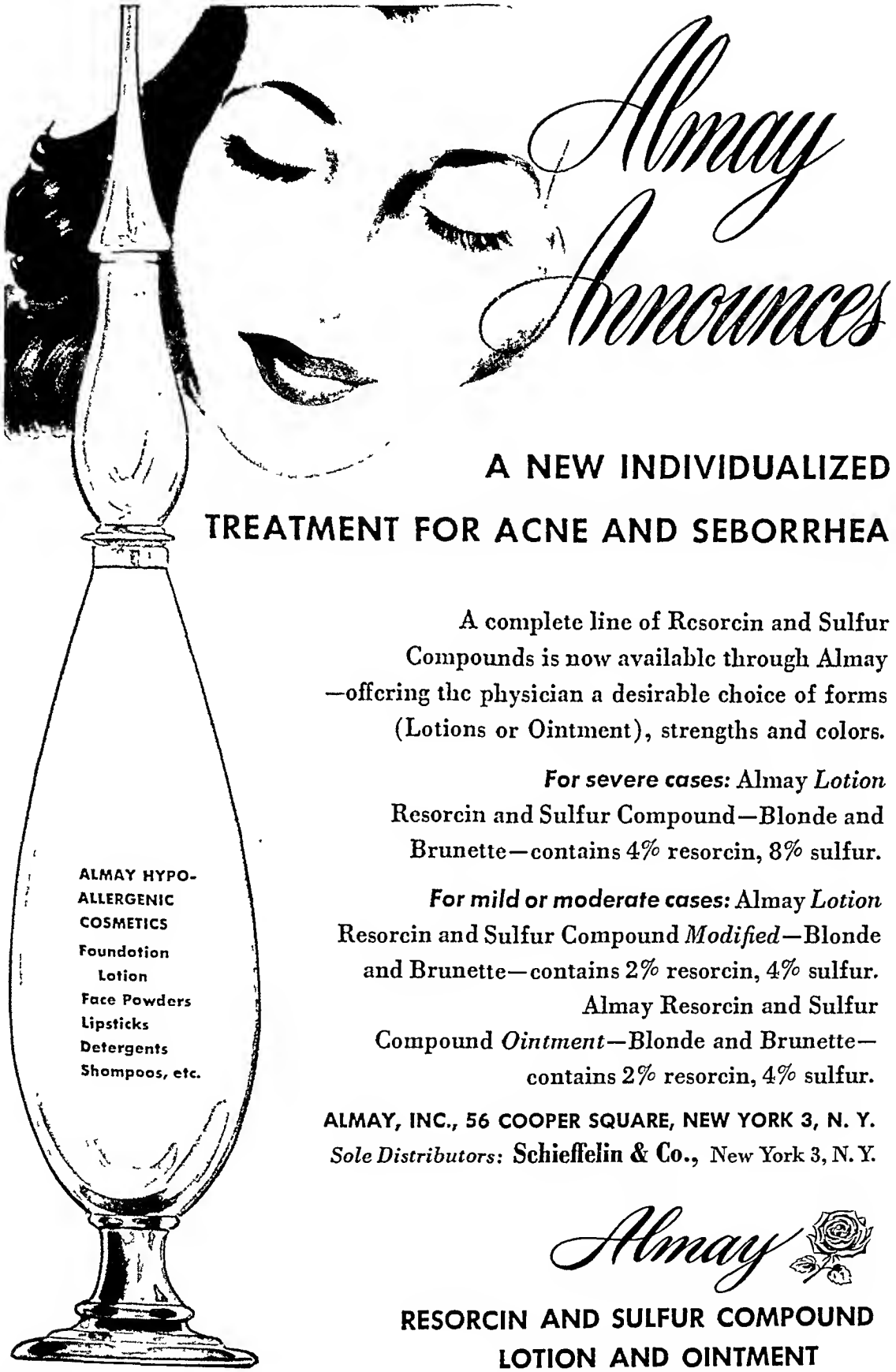

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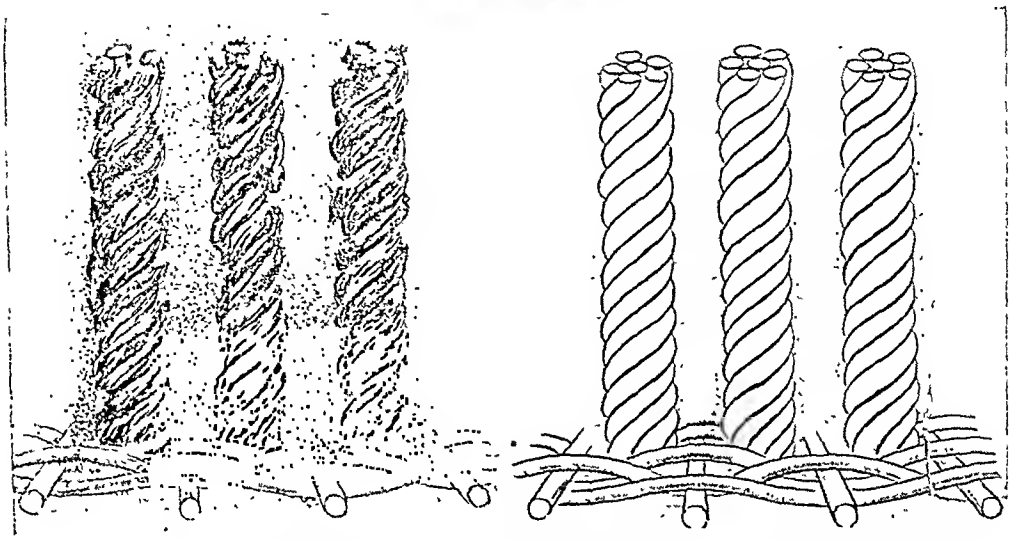

Artist's drawing of three wool strands, highly magnified, shows:

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*A. F. Coca, Annals of Allergy, Sept.-Oct., 1948.

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(See page 71)

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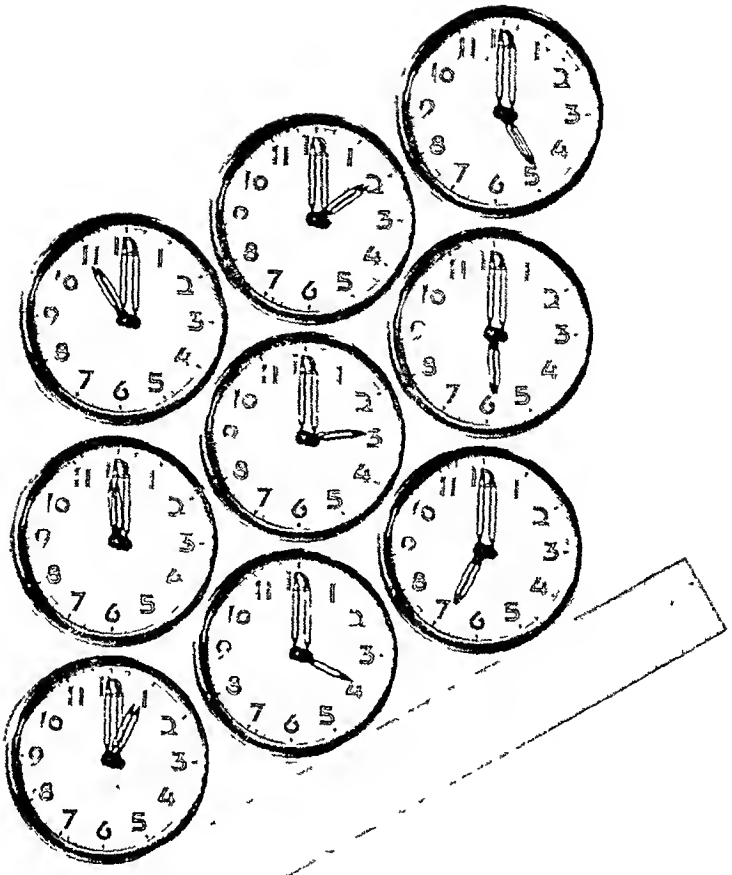

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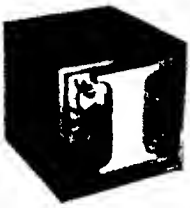

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1 Jones, B. B.: Virginia Med. Monthly, 74:241, June, 1947.
2 Levine, S. Z.: J. A. M. A., 128:283, May 26, 1945.
3 Schroeder, L. J. et al.: J. Nutrition, 32:413, Oct., 1946.

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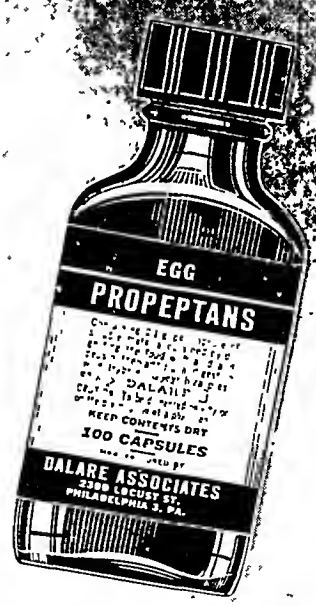

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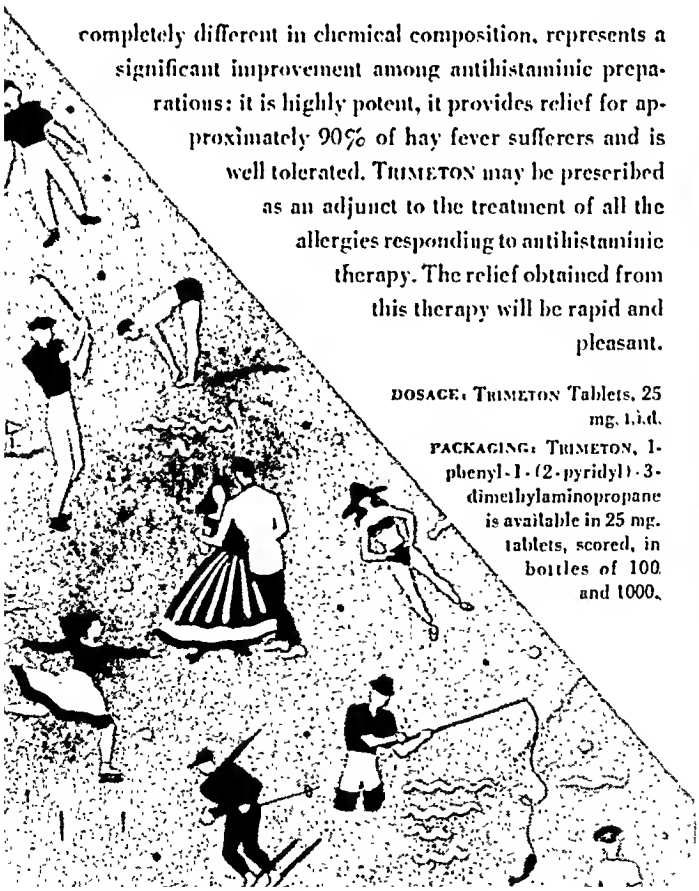

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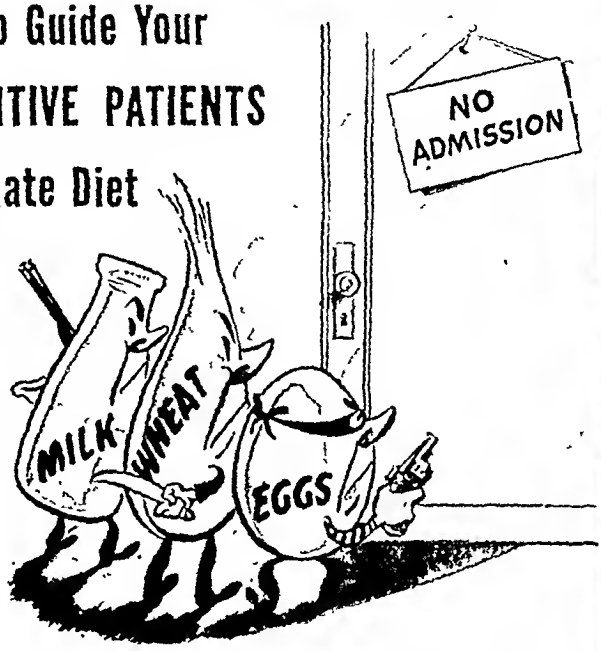

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*Stillians, Arthur W.; Concealment of Cutaneous Blemishes, Arch. Derm. & Syph. 57: 279 (Feb.), 1948

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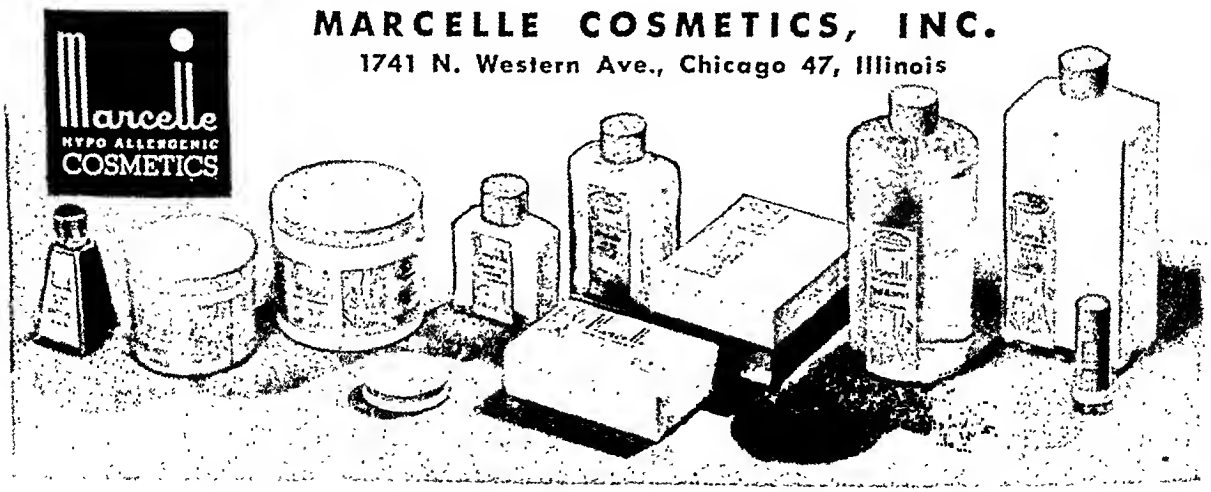

COSMETICS FOR ALLERGIC AND SENSITIVE SKINS

ANNALS of ALLERGY

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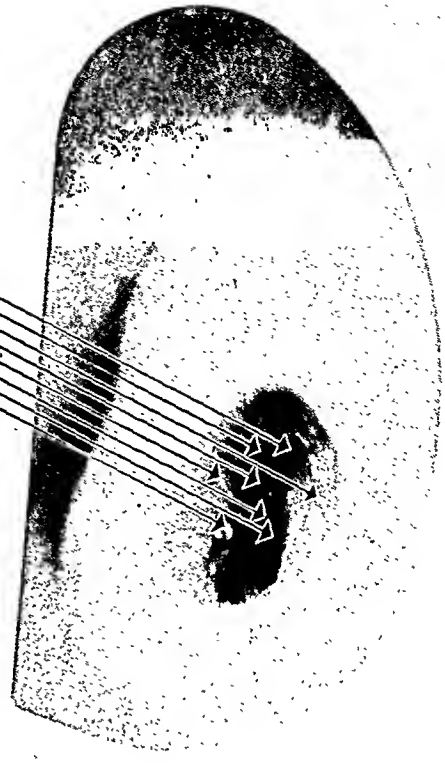

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ANNALS of ALLERGY

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IMMUNOLOGICAL STUDIES WITH SERA FROM PENICILLIN-ALLERGIC PATIENTS

M. SALAZAR MALLEN, F.A.C.A. (Hon.), F.A.C.P., and OFELIA CUELLAR, Q.F.B.
Mexico City, Mexico

DUE possibly to its low molecular weight, penicillin has been shown to have a weak and irregular ability to act as an anaphylactogen,[6] while allergic reactions after its use have been reported in only from 2 to 5.7 per cent of penicillin-treated individuals.[4,5] Symptoms attributable to penicillin allergy are more or less typical, having in most cases the appearance of the serum reactions. Eczematous, vesicular and exfoliative eruptions, have also been described so as to make the clinical diagnosis in some instances easily confused with a number of other allergic and toxic syndromes.[2,3]

The studies here reported deal with the search for antibodies for pure (crystalline "G") and amorphous (yellow) penicillin in the sera of patients showing or having shown allergic reactions to the drug.

Penicillin antigens.—Collodion particles, prepared according to Cannon and Marshall,[1] were sensitized with crystalline "G"* and amorphous penicillin, in order to make two antigens, as follows:

To 10 c.c. of the stock suspension of collodion, are added 20 c.c. of the penicillin (sodium salt) in 0.85 per cent saline solution, containing 500 I.U. per c.c.; the mixture is shaken by hand and left overnight in the ice-box. Before its use it is centrifuged for three minutes at 2,500 r.p.m.; the sedimented particles are washed once with saline and resuspended to give a No. 5 turbidity with McFarland's scale.†

The reaction was carried out by mixing, in two series of serological test tubes, 0.2 c.c. of each antigen and 0.2 c.c. of fresh (unactivated)** serum in dilutions from 1:10 to 1:1280.

From the Allergic Unit, Hospital General, and the Laboratories, Instituto N. de Cardiología, México D. F.

*Pure penicillin "G" was donated by Glaxo Laboratories, London.

†A recent paper by Caveti (J. Immunol., 57:141, 1947) gives some [illegible] of collodion agglutination; we have adhered to these in our later studies.

**Caveti recommends the use of inactivated sera.

TABLE I. AGGLUTINATION OF COLLODION SENSITIZED PARTICLES WITH THE SERA OF 15 PENICILLIN ALLERGIC INDIVIDUALS

Cases	Antigen	Agglutinating Titer						Remarks
		1/10	1/20	1/40	1/80	1/160	1/320	
1	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	++	++	—	—	Penicillin urticaria
2	C.P.	—	—	—	—	—	—	Urticaria and edema.
	A.P.	+++	+++	+++	++	—	—	Joint swelling.
3	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	++	—	—	Urticaria
4	C.P.	—	—	—	—	—	—	Urticaria and edema.
	A.P.	+++	+++	+++	++	—	—	
5	C.P.	—	—	—	—	—	—	Contact dermatitis flare up
	A.P.	+++	+++	+++	++	—	—	and positive patch test.
6	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	++	—	—	Mild urticaria.
7	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	+	+	—	Severe urticaria
8	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	—	—	—	Urticaria.
9	C.P.	—	—	—	—	—	—	Urticaria, joint symptoms,
	A.P.	+++	+++	+++	+	—	—	arrythmia.
10	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	++	—	—	Urticaria.
11	C.P.	—	—	—	—	—	—	Giant edema, severe
	A.P.	++	+	+	+	—	—	urticaria.
12	C.P.	—	—	—	—	—	—	Physician, said to be
	A.P.	—	—	—	—	—	—	allergic to penicillin.
13	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	—	—	—	Severe urticaria.
14	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	—	—	—	—	Urticaria.
15	C.P.	—	—	—	—	—	—	
	A.P.	+++	+++	+++	++	+	—	Urticaria and edema.

C.P.—Crystalline penicillin used to sensitize collodion.
A.P.—Amorphous penicillin used to sensitize collodion.
25 samples used as control (sera of non-allergic individuals) as well as non-sensitized collodion with "allergic sera", were all negative.

Control tubes were also set up, with collodion particles sensitized with crystalline and amorphous penicillin and normal sera, and nonsensitized collodion with saline, normal and "penicillin allergic" sera.

All tubes were individually shaken by hand, and left overnight in the icebox. Readings were made after adding to each tube 0.50 c.c. of saline solution and centrifuging for three minutes at 1,500 r.p.m.

The results were noted by taking into consideration the formation of agglutinated particles and the turbidity of the suspension. Readings were made after shaking each tube at the bottom, trying to suspend the sedimented collodion particles. The negative tubes presented a uniformly turbid suspension; weak positives (+) showed fine agglutination in an opalescent suspension, very much like a weak Kahn reaction; positive ones (++) showed gross particles floating in a very slightly opalescent suspen-

sion, while strong positives (+++) consisted of coarse granules that did not get into suspension in the clear supernatant liquid.

Data presented in Table I show the results obtained by studying the sera of fifteen penicillin-allergic individuals.

COMMENT

Demonstration of penicillin hypersensitiveness is attempted by performing intradermal or patch tests with penicillin solutions. Positive responses of the immediate (urticarial) or late (tuberculin-type) as well as eczematous changes are inconstantly seen.

By using the technique of agglutination of penicillin-sensitized collodion particles, it has been possible, in accord with our studies, to demonstrate agglutinating properties against the collodion antigen with amorphous penicillin in fourteen out of fifteen sera of "penicillin allergic" individuals. It is of interest to emphasize that collodion particles sensitized with crystalline penicillin were not agglutinable, suggesting that in our cases antibodies were present against impurities contained in "amorphous" penicillin. In a case (No. 5) of a highly sensitive laboratory worker, that showed clinical symptomatology of the contact type, antibodies were demonstrated against amorphous penicillin but not for the pure crystalline drug; the patient, however, gave strong cutaneous (eczematous) reaction with both penicillins. The reason for this result is not clear, but it is reasonable to assume that skin sensitizing antibodies may exist in the skin cells in absence of circulating ones.

REFERENCES

1. Cannon, and Marshall, P. R.: J. Inmunol., 38:365, 1940.
2. Goldman, L.; Friens, F., and Mason, L. M.: J.A.M.A., 131:883, 1946.
3. Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Arch. Dermat. & Syph., 50:6, 1944.
4. Keefer, C. S.: J.A.M.A., 122:1217, 1943.
5. Lyons, C.: J.A.M.A., 123:1007, 1943.
6. McClosky, W. T., and Smith, M. I.: Proc. Soc. Exper. Biol. & Med, 57:270, 1944

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SENSITIVITY REACTIONS FROM PENICILLIN PREPARATIONS OF PROLONGED ACTION

EDGAR A. HAUNZ, M.D., M.S. (Med.), and ERNEST L. GRINNELL, B.S., M.D.
Grand Forks, North Dakota

IN the past four years penicillin has been administered parenterally in various suspension media which retard the absorption of the drug and thereby maintain demonstrable blood levels for twelve to thirty-six hours from a single injection. The first to succeed in prolonging the action of penicillin were Romansky and Rittman,[11,12] who in 1944 described a method of prolonging the action of penicillin by suspending it in a mixture of beeswax and peanut oil. This preparation gained wide acceptance and has been proven to be both therapeutically effective and practicable. In 1946 Romansky[9] published an extensive report on the results of treatment with penicillin in beeswax and peanut oil. In this report the statement was made that the incidence of allergic reactions after intramuscular injection of calcium penicillin in beeswax and peanut oil was approximately 5 per cent. It is the purpose of this paper to present evidence from an investigation of 142 patients that the incidence of allergic reactions is probably considerably higher than 5 per cent and that these reactions may be very severe and sometimes generalized.

Distinct advances have been made recently in the preparation of procaine penicillin salts suspended in sesame or peanut oil, which, on the basis of preliminary reports, are successful in achieving the same prolongation of action as the former beeswax mixtures, but with apparently negligible allergic reactions or irritation. More recently, preparations of crystalline procaine penicillin G mixed with a hydrophilic colloid (carboxy-methyl cellulose), which can be injected in aqueous suspension, have appeared on the market. The early use of these preparations was attended by technical difficulty, in that the needle sometimes plugged before the injection could be completed. This objection has been largely overcome by improvements in manufacturing techniques, such as reduction of particle size, and the incidence of plugging has been less than 5 per cent with the latest batches.

SENSITIVITY PHENOMENA

Reactions from penicillin were more common in earlier days when preparations of the drug contained many impurities. Chief among these impurities were the so-called pyrogens. In fact, when penicillin was first commercially available, the product was so crude that the actual potency of the penicillin fraction was less than a tenth of that which obtains in present-day products. It had been demonstrated that tissue sensitivity developed in 2 or 3 per cent of non-allergic patients and in a larger number of allergic or previously treated individuals. Earlier reactions were very

From the Department of Internal Medicine, Grand Forks Clinic.

severe and included urticaria, dermatitis, chills, fever, abdominal cramps, vomiting, convulsions, depression or excitation, purpura, azotemia, and hematuria, depending somewhat upon whether the drug was given subcutaneously, intramuscularly or intravenously. Most of these reactions, with the exception of cutaneous manifestations, are no longer seen.[1] Indeed, it has been shown that the quantity of penicillin administered bears no direct relationship to the incidence or hazard of reactions. Four million units have been given daily with no ill effects. In 1943, Lyons[6] found urticaria to be the commonest allergic manifestation to penicillin, occurring in 5.7 per cent of 209 cases. It is very likely that the incidence is considerably lower now that penicillin is available in the purest form. The refinement of technique in manufacture, which has been so remarkably achieved over a period of a few years, is a noteworthy contribution of the pharmaceutical industry.

It is of interest that crystalline penicillin G in its dry form is stable for many years. Apparently it is not a strong allergen. Feinberg[3] demonstrated that individuals sensitive to penicillin spores did not give a positive reaction to penicillin. This would seem to indicate that there is no cross-sensitization to penicillin and the penicillium spores. Boufort and Olansky[2] emphasized the low incidence of reactions in persons receiving crystalline penicillin even though these persons had experienced variable reactions from non-crystalline penicillin previously given. Similar observations were reported by Welch et al[17] in 1945. In summary, it may be stated that allergic or sensitivity reactions to crystalline penicillin G are infrequent, and while no exact figure seems to be available, the incidence is certainly far below the 5.7 per cent reported by Lyons[6] in 1943 when penicillin was available in crude form only. According to Rockwell,[8] oral penicillin in adequate dosage is more liable to produce sensitivity reactions to penicillin than any other method of administration. We therefore do not believe it unusual that not a single instance of allergy to crystalline penicillin G *per se* was encountered in our study of 142 patients.

Reactions, both irritative and allergic, from penicillin-oil-beeswax are frequent and have been thought to be due in most instances to some protein-like material in the beeswax. The preparation of penicillin-oil-beeswax used in this investigation contained 4.8 per cent beeswax.

According to Sulzberger,[15] beeswaxes contain extractives from different kinds of flowers and plants according to where the bees feed. American beeswax sometimes contains sufficient oleoresins of ragweed to give positive reactions to patch tests in ragweed-sensitive persons. On the other hand, Gay[4] stated that no reaction occurred by scratch or intracutaneous tests with 4 per cent beeswax in peanut oil mixtures in thirty-one patients with clinical hay fever or asthma due to pollens, crude, unfiltered or filtered.

The mixtures of procaine penicillin G in sesame oil or in peanut oil have been shown by Herrell[5] and others[13,14] to possess essentially the same

capacity for prolongation of action of penicillin as that which obtains from the earlier beeswax suspension. There has been some controversy concerning the relative merits of peanut oil versus sesame oil in preparation and use of these mixtures. The authors have found little argument for or against either substance on the basis of allergenic or irritative tendency. Only occasional instances of sensitization to peanut oil or to sesame oil have been mentioned.[8,10] While it may be stated that procaine penicillin G in peanut oil or sesame oil is fast becoming well established as an effective and nontoxic preparation, the cumulative data relative to the newer procaine penicillin G in aqueous suspension are as yet too meager for authoritative comment on effectiveness, utility and innocuousness.

In various reports,[7,9,16] the incidence of local or systemic reactions from penicillin-beeswax-peanut-oil mixtures appears to be almost negligible. At least three reasons may be stated which render this low incidence very doubtful. (1) The number of cases reported is too small in each series for reliable conclusions. (2) Patients were studied primarily for blood levels of penicillin and therapeutic effectiveness, not specifically for irritative or allergic phenomena. (3) Reactions could be overlooked from lack of adequate follow-up, since patients frequently fail to call attention to minor reactions unless specific inquiry is made.

In our opinion, skin reactions to procaine itself are extremely rare.

CLINICAL STUDIES

Three penicillin preparations* of prolonged action were utilized in treating a total of 142 ambulatory patients at the Grand Forks Clinic. The purpose of this investigation was twofold, namely, (1) to determine the incidence and severity of reactions which obtain from the use of these preparations, and (2) to encourage total abandonment of calcium penicillin in beeswax and peanut oil because we are convinced that this preparation has now been superseded by at least one superior mixture.

Of the total of 142 patients receiving injections of penicillin, 100 received calcium penicillin in beeswax and peanut oil (Romansky formula), sixty-three received procaine penicillin G in peanut oil and seventeen received procaine penicillin G (Wycillin) in aqueous suspension. The total appears to exceed 142 patients because thirty-eight patients received one or more injections of penicillin-oil-beeswax in the left buttock and one or more injections of procaine penicillin G in peanut oil in the right buttock in 300,000 unit-doses for purposes of comparison of the two in the same patient. No patient received less than two 300,000 unit injections of whatever preparation was used in each instance, except in the case of a two-year-old child.

The patients' ages ranged from two weeks to seventy-two years. There were eighty-six male and fifty-three female patients.

*The authors are grateful to the research division of Wyeth Incorporated and especially to Dr. Edward F. Roberts, Director of Clinical Investigation, for supplying: (1) calcium penicillin (amorphous) in beeswax and peanut oil (Romansky formula), (2) procaine penicillin G (crystalline) in peanut oil with aluminum monostearate, and (3) Wycillin, a new preparation of crystalline penicillin G for injection in aqueous suspension.

TABLE I. TENDERNESS TO PRESSURE AT INJECTION SITES IN 142 PATIENTS GRADED ON BASIS OF IV

	Grade I	Grade II	Grade III	Grade IV
Calcium penicillin (amorphous) in beeswax and peanut oil.....	52 of 100 patients	13 of 100 patients	9 of 100 patients	3 of 100 patients
Crystalline procaine penicillin G in peanut oil	2 of 63 patients	None	None	None
Crystalline procaine penicillin G for aqueous injection (17 patients)....	None	None	None	None

Grade I = Mild tenderness
Grade IV = Extreme tenderness

Eleven of the total of 142 patients gave histories of allergy to substances other than ingredients used in this investigation. Of these eleven patients, two developed sensitivity reactions to penicillin in beeswax and peanut oil. These two had in the past reacted to wool clothing and to "a scarlet fever injection," respectively. Of the 100 patients receiving calcium penicillin in beeswax and peanut oil, eleven (11 per cent) developed sensitivity reactions. In two patients the end result was generalized, bilaterally symmetrical urticaria with intense pruritus, malaise, and, in one patient, abdominal cramps. In another patient an erythematous maculo-papular rash developed in both groins and in the medial aspect of the upper one-third of both thighs. In the remaining eight patients, various urticarial reactions developed at the sites of injection of calcium penicillin in oil and wax, accompanied by varying degrees of tenderness to pressure and pruritus. It may be concluded from Table I that seventy-nine patients experienced tenderness at the sites of injection in varying degrees of intensity, which in only two instances resulted from injections of procaine penicillin G in peanut oil.

Of the total of sixty-three patients who received procaine penicillin G in peanut oil only one reaction occurred, and this consisted of a mild transient macular erythema, 3 cm. in diameter, accompanied by Grade I tenderness and pruritus. In this particular patient a severe sensitivity reaction had followed an earlier injection of calcium penicillin in beeswax and peanut oil, involving the entire left buttock and accompanied by Grade III tenderness and pruritus. A second injection of procaine penicillin G in oil one week later in the site of the previous reaction in the right buttock (to procaine penicillin G in oil), failed to produce any type of reaction in this patient. Of the seventeen patients who were injected with crystalline procaine penicillin G in aqueous suspension, not a single instance of reaction or irritation was observed. (This, of course, is too small a group from which to draw reliable conclusions.)

Space forbids our reporting in detail each of the eleven patients who developed reactions. Therefore, three cases are presented and these represent the most severe reactions encountered.

CASE REPORTS

Case 1.—The patient, a man aged twenty-eight years, was seen in the clinic with an infection of the third finger of the right hand. Careful inquiry revealed no

previous allergies of any kind. He was given two injections of penicillin-oil-beeswax in the left buttock and two injections of procaine penicillin G in peanut oil in the right buttock. The last injection given was penicillin-oil-beeswax, and four hours later there developed a generalized, bilaterally symmetrical urticaria involv-

Fig. 1. (Case 1) Generalized bilaterally symmetrical urticarial lesions beginning on the flexor surfaces of the forearms and just below the groin areas in a man aged twenty-eight years who developed sensitivity to beeswax a few hours after injection. Practically the entire surface area of the body was involved sixteen hours after this picture was taken.

ing the hands, flexor and extensor surfaces of the arms and forearms, scalp, face, trunk, abdomen, groins, extensor surfaces of the knees, and feet (Fig. 1). Eight hours after the last injection, practically the entire surface area of the body was involved, and the patient complained of malaise, intense pruritus and severe cramping abdominal pains.

On physical examination the left buttock was intensely red over an area approximating 6 inches in diameter, the center of which corresponded to the site of injection of penicillin-oil-beeswax and was tender, Grade IV, to pressure. The right buttock disclosed urticarial lesions similar to those found on the rest of the body. His temperature and blood pressure were normal. The patient was hospitalized and given 50 milligrams of Benadryl every six hours, with an injection of 5 minims of adrenaline every three hours, and remarkable improvement was noted in twelve hours. After sixteen hours there was apparent total recovery so the patient was dismissed. However, the following day he returned to the clinic in what appeared to be a drunken stupor, although he had not imbibed any alcohol. Physical examination revealed a total recurrence of generalized urticaria superimposed on which was severe angioneurotic edema, most pronounced on the face, hands, scrotum and feet (Figs. 1, 2, and 3). Again he complained of severe abdominal pain. He was readmitted to the hospital, the same treatment instituted, and again there was apparent complete recovery. It is of interest that this patient had received penicillin-peanut-oil-beeswax on three different occasions in the past four years without untoward effects.

An intramuscular injection of 30,000 units of calcium penicillin (amorphous) in normal saline was given intramuscularly following subsidence of the reaction and no signs of sensitivity to penicillin developed. Also, an intramuscular injection of 1 c.c. of sterile peanut oil produced no irritative or allergic phenomena.

Case 2.—The patient, a woman aged eighteen, was seen in the clinic and a diagnosis of pneumonitis in the right mid-lung was made. Careful inquiry revealed a history of urticarial sensitivity to wool clothing. The patient received a series of

Fig. 2. (Case 1) Normal facies of patient before angioneurotic edema developed.

Fig. 3. (Case 1) Typical facies of angioneurotic edema which developed twenty-four hours after two injections of penicillin-oil-beeswax. Remarkable improvement followed the administration of adrenaline and Benadryl.

ten injections of penicillin in oil and beeswax in both buttocks without any untoward effects except for Grade III tenderness bilaterally at the sites of injection. Because of persistence of the chest lesion and low grade fever, she was given another course of eight daily injections of penicillin-oil-beeswax, i.e., four injections in each buttock. Following the sixth injection of penicillin-oil-beeswax, small areas of erythema appeared over the injection sites. Within three days after the last injection, the areas of erythema had enlarged bilaterally to a diameter of approximately 6 inches, accompanied by Grade IV tenderness to pressure, intense localized pruritus and general malaise (Fig. 4). Because the patient was not in extreme discomfort, it was decided not to give her any treatment for the reaction. In this instance, five days were required for complete disappearance of the areas of erythema and pruritus, but the tenderness persisted for eleven days.

An intramuscular injection of 30,000 units of calcium penicillin (amorphous) in normal saline was given following subsidence of the reaction and no signs of sensitivity to penicillin developed. Also, an intramuscular injection of 1 c.c. of sterile peanut oil produced no irritative or allergic phenomena.

Case 3.—A female child, aged two years, was brought to the clinic and a diagnosis of infected tonsils was made. The parents had observed no previous allergic reactions in the patient. A single injection of the usual dose of 300,000 units of penicillin-peanut-oil-beeswax was administered in the upper outer quadrant of the left buttock. Seven days later the first signs of irritation appeared as a rapidly expanding area of raised erythema which finally involved practically the entire right buttock (Fig. 5). As nearly as could be determined in a child of this age, there was tenderness Grade III to pressure, and the child constantly attempted to scratch the area. No treatment was given and the reaction subsided completely in sixteen days.

An intramuscular injection of 30,000 units of calcium penicillin (amorphous) in normal saline failed to produce any signs of irritation. It is of interest that this patient had received no previous injections of penicillin. Also, an intramuscular injection of 1 c.c. of sterile peanut oil produced no irritative or allergic phenomena.

Fig. 4. (Case 2) Areas of intense raised erythema following eight injections of penicillin-oil-beeswax in a female patient aged 18.

Fig. 5. (Case 3) Severe reaction of raised erythema involving practically the entire right buttock in a female child aged two years, occurring seven days after a single injection of penicillin-oil-beeswax.

COMMENT

It has been shown that of the three preparations utilized in this investigation, calcium penicillin (amorphous) in beeswax and peanut oil (Romansky formula) was the mixture which produced frequent sensitivity reactions, with the exception of one relatively mild and quite transient reaction to procaine penicillin G in peanut oil which was encountered in one patient. This patient had experienced a severe reaction to penicillin-oil-beeswax eight days previously. A second injection of procaine penicillin G in peanut oil failed to produce any irritative effects.

It is true that while 100 patients received penicillin-oil-beeswax, only sixty-three were given procaine penicillin G in peanut oil. It is unfortunate that the latter preparation could not have been given likewise to 100 patients, but this newer preparation was not available until some time after the investigation had been under way primarily to study sensitivity reactions to the beeswax mixture. Nevertheless, it is worthy of emphasis that beeswax was believed to be the instigator of all the reactions encountered except one, as evidenced by the following criteria: (1) Of all thirty-eight patients who received alternate injections of penicillin-oil-beeswax and procaine penicillin G in peanut oil (in opposite buttocks as previously described), five patients had moderate to severe reactions to the beeswax preparation, while none reacted to the procaine penicillin G in peanut oil, with the exception of one patient who reacted mildly to the latter as well. (2) In each of the eleven cases manifesting reactions, a separate intramuscular injection of 1 c.c. sterile peanut oil was given after the reaction subsided and in no case produced any allergic phenomena. (3) Similarly, each of the eleven reactive patients was also given an intramuscular injection of 30,000 units of calcium penicillin (amorphous) in physiological saline, and no reaction occurred. *Sine qua non* proof that beeswax effected these reactions could probably be established by administering an intramuscular injection of beeswax vehicle to each of the reac-

tive patients. This was avoided primarily because of the risk which may well attend such a procedure. It would hardly seem necessary to resort to such radical measures when rather convincing evidence has been presented by the process of exclusion. Skin tests were not resorted to for similar reasons. The fact that two of the eleven reactive cases had definite allergic histories suggests that sensitivity reactions to penicillin-oil-beeswax may be more common among patients with other allergies. The addition of procaine to the newer preparation of penicillin is indeed a significant advance, in retrospect of the frequency with which considerable tenderness follows the injection of penicillin-oil-beeswax (Table I).

Procaine penicillin G in aqueous suspension promises to be the ideal preparation of prolonged action in view of the absence of tenderness or irritative phenomena in this small series of seventeen cases.

The fact that a severe reaction to a single injection of penicillin-oil-beeswax was encountered in a child two years of age with a negative allergic history and no known previous exposure to either penicillin or beeswax suggests that previous sensitization to the allergen is not mandatory.

As in serum sickness, a single injection of the antigen is sufficient to produce sensitization as well as to elicit the sensitivity reaction after a suitable incubation period.

SUMMARY AND CONCLUSIONS

1. Preparations of calcium penicillin (amorphous) in beeswax and peanut oil (Romansky formula), procaine penicillin G (crystalline) in peanut oil and aluminum monostearate, and procaine penicillin G (crystalline) in aqueous suspension have been studied in a total of 142 patients for the sole purpose of evaluating their capacities to produce sensitivity reactions.

2. Eleven of 100 cases given penicillin-oil-beeswax developed moderate to severe and generalized skin reactions. One mild transient reaction was observed from procaine penicillin G in peanut oil. No reactions or tenderness occurred in seventeen cases receiving procaine penicillin G in aqueous suspension.

3. Evidence has been presented to indicate that all reactions except one were due to beeswax and, because at least one superior mixture is now available, total abandonment of calcium penicillin in beeswax and peanut oil is encouraged.

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REFERENCES

1. Anderson, D. F. Treatment of infections with penicillin. New England J. Med., *232:423-429, 1945.*
2. Boufort, S. W., and Olansky, Sidney: Report of patient tolerating crystalline penicillin without reaction after repeated cutaneous reactions to crude penicillin. North Carolina M. J., 8:82-83, (Feb.) 1947.

3. Feinberg, S. M.: Penicillin allergy. J. Allergy, 15:271, (July) 1944.
4. Gay, L. N.: The nonantigenic property of beeswax. J. Allergy, 16:192-195, 1945.
5. Herrell, W. E.; Nichols, D. R., and Heilman, F. R.: Procaine penicillin G (Duracillin): A new salt of penicillin which prolongs the action of penicillin. Proc. Staff Meet., Mayo Clin., 22:567, (Dec. 10) 1947.
6. Lyons, C.: Penicillin therapy of surgical infections in the U. S. Army. J.A.M.A., 123:1007-1018, (Dec. 18) 1943.
7. Nichols, D. R., and Haunz, E. A.: Prolonged action of penicillin in mixtures of beeswax and peanut oil. Proc. Staff Meet., Mayo Clin., 20:403-407, (Oct. 31) 1945.
8. Rockwell, G. E.: The letters of the International Correspondence Society of Allergists. Series XI, p. 79.
9. Romansky, M. J.: The current status of calcium penicillin in beeswax and peanut oil. Am. J. Med., 1:395-411, (Oct.) 1946.
10. Romansky, M. J., and Rein, C. R.: Treatment of early syphilis with calcium penicillin-oil-beeswax. J.A.M.A., 132:851, (Dec. 7) 1946.
11. Romansky, M. J., and Rittman, G. E.: A method of prolonging the action of penicillin. Science, 100:196-198, (Sept. 1) 1944.
12. Romansky, M. J., and Rittman, G. E.: Penicillin. 1. Prolonged action in beeswax-peanut oil mixture. 2. Single injection treatment of gonorrhea. Bull. U. S. Army M. Dept., No. 81, pp. 43-49, (Oct.) 1944.
13. Stollerman, G. H., Roston, E. H., and Tolearsky, B.: A guide to the use of procaine penicillin in hospital practice. New York J. Med., 48:2501-2505, (Nov. 15) 1948.
14. Sullivan, N. P.; Stymmes, A. T.; Miller, H. C., and Rhodehamel, H. W., Jr.: A new penicillin for prolonged blood levels. Science, 107:169-170, (Feb. 13) 1948.
15. Sulzberger, W.: J.A.MA.., 132-851, (Dec. 7) 1946.
16. Trussell, P. C.; Sinclair, A. B., and Buchanan, S. C.: Duration of effective blood levels following administration of penicillin in peanut oil and beeswax. Canad. M. A. J., 57:387, (Oct.) 1947.
17. Welch, H., and Rostenberg, A., Jr.: Hypersensitivity of the tuberculin type to crystalline penicillin. J.A.M.A., 126:10-12, (Sept. 2) 1944.

1949 FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

The 1949 Fall Graduate Instructional Course in Allergy will be conducted under the auspices of Baylor University School of Medicine, Houston, Texas, October 31 through November 5. This will be a five and one-half day course. Instructors of outstanding ability are already being selected for the faculty. The diagnosis and treatment of allergic diseases, as well as the basic sciences pertaining to allergy, will be presented. Round-table discussions will occupy two evenings.

Both members and non-members are cordially invited to attend. The headquarters will be at the beautiful new Shamrock Hotel. The price for this course will be $100.00. Detailed information may be obtained by writing to Dr. Homer E. Prince, Medical Arts Building, Houston, Texas, Chairman and Director of the Instructional Course Committee.

A REVIEW OF THE CHEMICAL APPROACH TO ALLERGENS

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A REVIEW of the early chemical contributions is a prerequisite for a just evaluation of the more recent studies of allergens and of their clinical import.

July 13, 1865, marked a memorable event in the history of allergy. On that day, Charles Harrison Blackley[12] of Manchester, England, performed upon himself the first diagnostic skin test for hay fever. He then proved that the pollen of the grasses was responsible for the English type of hay fever. In 1903, Dunbar,[22] who had accepted the English view concerning the pollen origin of hay fever, demonstrated that the protein constituent of the pollen grain was the toxic agent. In 1904, Kammann,[37] a pupil of Dunbar, published the first chemical analysis of rye pollen, which is the most important cause of hay fever in Germany. Kammann's conclusion that the albumin of the pollen grain is the toxic factor, is indeed, significant. According to the method of extraction employed by the author, it is likely that he was dealing with a mixture of proteose and albumin. No mention of proteose as such is made, nor is the clinical evidence cited upon which the toxicity of the albumin fraction is based.

Wolff-Eisner,[64] in a monograph published in 1906, made the suggestion that hay fever might result from a protein sensitivity. During the succeeding eight years, evidence was gradually accumulated to indicate that the protein was the active constituent of pollen grains. This consideration induced Cooke to standardize his pollen extracts on the basis of total nitrogen which they contained. The contributions of Heyl[30,31] (1917, 1919) have been of special value. He isolated from the pollen of the short ragweed three important proteins: an albumin present to the extent of 1.2 per cent, a proteose present to the extent of 3 per cent, and a glutelin fraction. Heyl's investigations, despite their thoroughness from a chemical viewpoint, are of limited clinical value. The author reported that he had been obliged to remove a hay fever subject to the hospital because of the very severe reaction produced by an injection of a solution containing about 0.000,007 gram of albumin. This experience discouraged further clinical tests.

The following suggestions made by Heyl should prove of interest:

> "In the opinion of the writer, it remains for some large hay fever clinic to test out the various proteins, especially the proteose, and determine which of them may be responsible for hay fever. This proteose is unstable and becomes insoluble on preserving so that a very close co-operation must exist between the clinicians and those doing chemical work."

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In 1924, Bauman, Chudnoff and Mackenzie,[5] in their attempt to separate the active constituent of ragweed pollen, concluded by inference that it was in the form of a large molecule or aggregate. They designated the globulin fraction as the more active agent. These authors, it is to be noted, assumed the existence of a single "active constituent."

Interestingly enough, Caulfield[15] in 1925 made a report on "Skin Tests on Hay Fever Cases with Chemically Different Fractions from Ragweed Pollen." This report appeared simultaneously with one by Csonka, Bernton and Jones[20] on the isolation of chemically different fractions from timothy and orchard grass pollens; and in 1927 these authors[6] presented the following summary:

1. Four active proteins have been isolated from timothy pollen. These are designated proteose A, proteose B, albumin and glutelin.
2. Sixty-three per cent of vernal hay fever subjects show a cutaneous sensitiveness to two or more proteins. Twenty-one per cent are sensitive only to proteose A fraction, and 15 per cent only to the albumin.
3. The albumin constitutes one-ninth of the total extractable protein content.
4. The glutelin is of negligible importance.

In the preceding year, 1926, there appeared a study by Caulfield, Cohen and Eadie[16] on "The Antigenic Properties of Pollen Fractions." Under the caption "Chemistry of Timothy Pollen," Caulfield and his co-workers reported the isolation of proteose-albumin fraction, a proteose fraction and a glutelin. The albumin fraction itself had not been isolated by them, and therein exists the difference between their work and that of our own.

Grove and Coca, in 1923,[25] had sounded a discordant note, and expressed views most divergent from those which were commonly accepted. They subjected pollens to enzyme action. As a result of their experiments, they concluded that the active substance in pollen was not a protein in the usual sense of the term. Moreover, they showed that all of the nitrogen of a pollen extract could be eliminated by thorough enzymic digestion and dialysis without lessening the atopic activity.

The isolation of a soluble specific substance, a carbohydrate, from the pneumococcus by Heidelberger and Avery[28] was reported at the same time. This substance reacted with antisera in high dilutions. Accordingly, the idea that the active principle of pollen might be similar to the specific carbohydrate gained momentum. Black,[10] Caulfield,[17] Brown and Waters,[13] Service,[48] and Harley[26] of England appeared as champions of the new concept.

It is noteworthy that in the earlier experiments of Caulfield and his co-workers, and of Bernton, Jones and Csonka, the multiple nature of the active components of pollen grains upon susceptible persons was demonstrated.

The later work of Stull and associates,[59] of Abramson and his associates,[1] of Moore, Cromwell and Moore,[41] of Johnson and Rappaport,[35]

and of Hecht, Rappaport and Welker,[27] proved that more than one chemical fraction was involved in the production of skin reactions.

An outstanding publication by John M. Newell,[42] of Boston, entitled "A Review of Chemical Studies on the Allergens in Pollen," appeared in 1942. The bibliography includes 147 references. In his summary, the author makes the following assertions, in part:

> "The chemistry of the hay fever producing substance in pollens has been studied for about forty years. The sum of all this work is difficult to evaluate because of contradictory reports and lack of uniform methods for quantitative studies. . . . The activity is shared probably by several substances all of which are of complex chemical natures. . . . Some of the active substances contain much carbohydrate and others resemble proteins. They are inactivated by heat and alkaline media. . . . As yet, none of the active substances have been isolated in pure form in large enough quantities to permit a thorough chemical examination, so that their constitution is still not known exactly."

Furthermore, Newell in his paper, under the heading of "Active Proteins" states:

> "The protein nature of the active material of pollen has had its strong supporters. . . . The chemists of the United States Department of Agriculture have made considerable study of the proteins of agricultural products, especially cottonseed. The allergic phase of this work started by Jones and Csonka is still being carried on by Spies, Stevens and others in collaboration with Bernton and is mentioned here since the methods used may have a bearing on the study of pollens."

The reference made by Newell to the study of the allergens of cottonseed justifies a recapitulation of the successive phases of the investigation. The clinical implications of the study present a challenge to us as allergists.

Cottonseed was primarily selected because of the availability of material and its recognized potency as an allergen. In 1925, Jones and Csonka[36] first described methods for the isolation of the proteins of cottonseed, five in number. Their procedure involved successive extractions of the cottonseed with aqueous sodium chloride. In 1939, fourteen years later, Spies and his associates investigated the allergenic possibilities of these fractions. Skin tests, with four of the separated proteins and with two in combination, performed by us upon cottonseed-sensitive subjects, resulted in strongly positive reactions, with no evidence of differentiation in activity.

As fractionation progressed, it was soon recognized that the initial skin reactivity of the protein fractions was due to a contaminant. Accordingly the systematic alcohol fractionation of the water-soluble constituents of cottonseed was undertaken. It is noteworthy that as a result of a series of later experiments very active and specific fractions, designated CS-1 and CS-1A, have been isolated in quantities sufficient for chemical

analysis. Publications of the methods appeared in 1939[51] and 1940.[52] CS-1A represents approximately one per cent of the defatted cottonseed and contains 11.8 per cent nitrogen and 39.9 per cent polysaccharidic carbohydrate. By electrophoretic fractionation of CS-1A, a product, CS-51R, was obtained which contained 19.8 per cent nitrogen and only 0.9 per cent carbohydrate. Moreover, the high potency of the isolated fraction is manifested by the fact that the picrate of CS-1[53] induces positive reactions by intracutaneous injections of 0.01 c.c. of a $1:10^8$ solution in passively sensitized sites.

Newell's review, to which reference has been previously made, included the following statement: "The (allergic) activity is probably shared by several substances all of which are of complex chemical natures."

The polysaccharide protein fraction, CS-1, isolated from cottonseed was now available as a strategic determinant. Accordingly, a study[7] was initiated to ascertain whether the cottonseed allergen present in CS-1, or in the more highly purified pictrate derivative, CS-5, represented the sole allergen or only one of several water-soluble allergens of the cottonseed embryo. The following modification of the technique described by Lippard and Schmidt[38] was employed:

"Single sites were uniformly sensitized on the right upper arm of recipients by using 0.1 ml. of diluted or 0.05 ml. of undiluted serum from cottonseed-sensitive patients. After an interval of at least seventy-two hours, 0.5 ml. of a 1:1,000 solution of CS-5 was injected intramuscularly into the left arm of the recipient. Itching of the sensitized site was reported by the patients within a few minutes after the injection, and positive reactions developed in twenty to sixty minutes. After an interval of not less than seventy-two hours, the sensitized sites were tested for exhaustion of reagins specific for CS-5 by a second intramuscular injection of 0.5 ml. of 1:1,000 solution of CS-5 into the left arm of the recipient. In no instance was there a positive reaction at the sensitized site following this second test, thus indicating complete desensitization of reagins for CS-5 by the initial dose. After another interval of a minimum of seventy-two hours, a dose of unfractionated water extract was injected intramuscularly into the left arm. Positive reactions which developed in the sensitized sites following this injection of unfractionated aqueous extract indicated the presence of more than one allergen in cottonseed."

The serum from seven cottonseed-sensitive patients was studied in the foregoing manner. The reagins from three of the patients were completely neutralized by the isolated fraction, CS-5, whereas four sera contained reagins which reacted only upon the third injection of unfractionated cottonseed extract. These results indicate the presence of multiple cottonseed reagins and of multiple cottonseed allergens. The question of multiple allergens has been removed from the realm of probability to the realm of actuality.

In confirmation, the investigation of the nature of the unidentified allergens of cottonseed was a logical sequence.[54] Globulin fractions of cottonseed, 2CS-1 and 2CS-2, prepared after prolonged purification,

retained allergenic activity. Moreover, in the course of routine testing, two patients of extraordinary interest were encountered. They reacted positively when tested with whole cottonseed or unheated globulin preparations, and negatively when tested with fraction CS-1A or CS-51R. Their blood reagins were likewise specific for the globulin fraction.

In 1943, another advance was marked by the isolation and chemical characterization of the allergenic fraction, CB-1A, from castor beans by Spies and Coulson.[55] The procedure used in isolating CB-1A was similar to that developed independently for the isolation of the cottonseed allergen, CS-1A, in 1939.

The following summary of the properties of the castor bean allergen should be welcomed by clinicians and investigators in fundamental studies of allergy:

"CB-1A is a non-toxic, heat stable, dialyzable, polysaccharidic protein component of castor beans. It represents 1.8 per cent of the defatted castor bean meal.

"Chemical properties and amino acid content of CB-1A were remarkably similar to those of the previously characterized cottonseed allergen. Both CB-1A and CS-1A were characterized by relatively high proportions of arginine and cystine but CB-1A, in contrast with the cottonseed allergen contained no tryptophan. Both proteins also contained histidine, lysine, tryosine, and glutamic acid in addition to unidentified nitrogenous compounds in the monamino and dicarboxylic acid groups.

"The allergenic proteins of cottonseed and castor beans are composed of the usual amino acid components of ordinary proteins, but the molecular size of the allergenic proteins is much smaller than that of ordinary proteins. Thus the allergens of cottonseed and castor beans readily pass semipermeable membranes that are impermeable to ovalbumin."

In a later report,[56] a prolonged series of procedures is described whereby an essentially carbohydrate-free allergenic protein, CB-65A, has been isolated from fraction CB-1A, from castor beans. Heidelberger and Avery first noted the important role which carbohydrate played in the immunological specificity of the pneumococcus. Experiments revealed, however, that the fraction, CB-65A, exhibited the same antigenic specificity as CB-1A. CB-65A possessed a greatly diminished capacity to sensitize experimental animals, but the capacity to shock sensitized animals remained unaltered. The suggestion has been made that sensitization and shock may be produced by different functional groupings in the antigenic molecule. One grouping may, therefore, be altered without causing change in the other, or the carbohydrate may simply increase the size of the molecule and thus enhance the sensitizing capacity.

The presence in castor beans of a powerful toxic albumin, ricin, which rivals cobra venom in potency, is noteworthy. Consequently, aqueous extracts of castor beans are not suitable for intracutaneous diagnostic or investigative studies. Alilare,[33] who first described sensitivity to the castor oil plant, believed the allergen to be identical with ricin. Ricin and allergen CB-1A, are, however, distinct substances. Spies and Coulson

demonstrated that death in guinea pigs was produced in ninety-one hours by injection of 16 micrograms of total nitrogen from an unfractionated water extract of castor beans per kilogram of body weight. "However," the authors continued, "no primary toxic effect resulted in twenty-one days from injections of 5760 micrograms of CB-1A nitrogen per kilogram of body weight or 360 times the quantity of nitrogen from the unfractionated water extract which caused death."

Also of interest to the clinician is the observation that the allergen, CB-1A, is resistant to boiling water. Solutions of CB-1A may, therefore, be sterilized by heating at 100° C. on three successive days. Thus, losses incurred by absorption through the use of Seitz filtering pads for sterilization can be avoided.

It may not be amiss to cite presumptive evidence of the existence of another or other allergens in castor bean in addition to CB-1A. A member of the chemical staff who had assisted in the investigation of the castor bean had developed a sensitiveness. This was characterized by paroxysmal sneezing, coryza, lachrymation, swollen eyelids, wheezing, and dyspnea. On one occasion after exposure to castor bean dust, she stated: "The above symptoms were repeated, together with an inflamed throat, which was so swollen by evening that I could scarcely swallow. My voice became husky and at times failed altogether. Throat and eye symptoms remained for five days in lesser degree after the first twenty-four hours of acute discomfort." Other attacks have occurred when she entered a room where castor bean was being processed or when furniture moving stirred up dust. Cutaneous tests performed with CB-1A on the forearm of this worker were negative but a delayed reaction to castor bean hulls persisted for four weeks.

A remarkable physical property of the allergenic protein fractions, CS-1 and CB-1, isolated from the cottonseed and castor bean respectively, is their resistance to heat. Thus, CS-1, dissolved in water and autoclaved at 125° to 130° for an hour, gave positive cutaneous tests in the dilution 1:10.[5] Clinical evidence will now be presented to attest to the concept that the physicochemical characteristics of allergenic fractions not only vary from each other in different substances but vary from each other in the same substance.

A patient was tested by the cutaneous method with an extract of celery. The reaction was strongly positive. The typical wheal with pseudopod formation was accompanied with considerable itching. The patient then exclaimed: "That is what happens on my lips when I eat raw celery. But I can eat cooked celery as in soups without any trouble." It is apparent that one allergen in celery is heat-labile in contradistinction to the heat-stable allergens CS-1 and CB-1. The classic observation of Prausnitz and Kustner[13] in their work on passive transfer stands out in marked contrast. Kustner, it will be recalled, was fish-sensitive. Uncooked fish produced no allergenic disturbances in him, but fish when

cooked and subjected to a temperature of 55° C. became actively allergenic. In fact, cutaneous tests, positive with a boiled extract, provoked constitutional reactions.

By way of supplement, the case history of a male patient, aged forty-two, is cited. Ever since he was a boy of seven, he could not eat fish either in the raw or cooked state. Extensive angioneurotic edema developed within five to ten minutes after ingestion. He could, however, eat canned salmon or canned tuna fish without any untoward symptoms.

It may, therefore, be concluded from the foregoing clinical experience that the multiple allergens in fish show a difference in susceptibility to temperature changes. Some are active in the fresh state, some are activated by a temperature of 55° C. and all are inactivated by the temperature of the canning process. Fish are cold-blooded animals and their temperature is determined by that of their environment. This varies from the icy waters of the Arctic to the warm waters of the torrid zone. The question naturally arises whether allergens in fish vary with or conform to habitat.

The possibility of an allergen in volatile form now demands consideration. Feinberg and Aries[23] in 1932 reported cases of asthma which were provoked by exposure to the odor of cooking shrimp, peas and lentils. A case described by Spain,[50] in 1933, proved even more sensitive. It was that of a man who suffered from asthmatic attacks whenever he passed a fish market. More recently, Horesh[32] reported nine patients with infantile eczema, in whom acute exacerbations developed when eggs were opened or certain foods were fried in their presence. Another case report by the same author[33] is noteworthy. A boy aged four and one-half, began to cough and develop severe asthma when he ventured into the kitchen while the maid was peeling potatoes. The symptoms were also caused by the cooking of commercially canned potatoes. A patient of ours with an extreme sensitiveness to buckwheat invariably developed asthma in a very severe form upon entering an apartment house in which buckwheat cakes were being fried.

It follows, therefore, that the odors and vapors which are offending to some allergic individuals are specific in their action. Moreover, the sensitized cells of the skin or of the nasal mucosa are the points of contact with the allergen and serve as receptors. The chemical nature of the air-borne agent or agents, so potent and prompt in their reactions, invites investigation.

The multiplicity of allergens and their variability in physicochemical behavior as outlined above have contributed to the difficulty of testing for protein sensitization, especially for food sensitiveness.

Tuft, Blumstein and Wenger[62] have discussed, in a recent publication, the variations in allergenic activity of food extracts, and have reached the following conclusions:

1. "Different lots of food extracts, notably the fruits and vegetables prepared under standard conditions, were found to vary considerably in nitrogen content, apparently due to the inconstancy of the raw material.
2. "The allergenic activity of such extracts seemed to bear no constant relationship to their nitrogen content."

Happily, the methods elaborated by Spies and his co-workers make available allergenic substances free from many other complex organic constituents of the castor bean and cottonseed. The ultimate significance of their biochemical contributions cannot be overestimated. Thus a pattern has been designed for the determination of sensitiveness in man by testing with potent and stable allergenic entities. Confusion and controversy will diminish. It will tend to terminate the conflict between the schools of thought which advocate the cutaneous and intracutaneous methods of testing, respectively. The contradictory results obtained with the use of extracts, prepared according to diverse methods, will be eliminated, and the discrepancies in diagnoses made by allergists will no longer perplex patients.

We must give heed to the disconcerting analyses by Swineford and Weaver[60]; the need for more reliable clinical procedures becomes apparent from the following summary:

"In all, eleven symptom complexes were attributed by 200 people to forty-one foods or food groups 355 times. Of these the skin tests were negative in 285, positive in only seventy. On the other hand, there were 1,469 positive skin tests to foods to which the histories were negative."

Equally disturbing is the report made by Tuft of a comparative study of food extracts. He compared the results of testing patients with his own extracts and with the extracts of twelve commonly used food extracts from four other clinics. The sentiments, regarding testing for food sensitiveness to which earlier expression has been given, still prevail.

Gay summarizes this important phase of the subject as follows:

"Skin testing, although valuable in inhalant allergy, is not a particularly reliable diagnostic method in food allergy, as there is a high percentage of false negative and false positive reactions."

Rowe adds a disturbing note: "Subsequent intradermal testing with those (food) allergens which have failed to react by the cutaneous test has yielded confusing and little additional information of value." In 1928, he first published his "elimination diets." He is of the firm conviction that "trial diet" is of greater importance than skin testing.

Walzer assigns, among the reasons for this discrepancy between the clinical reaction and skin reaction of food allergens, the following:

"It is difficult to obtain an efficient and stable extract of some types of foods. . . . Skin tests are usually performed with extracts prepared from the raw foods,

but cooking may so alter the nature of many ingestants as to render them harmless. . . ."

No acceptable hypothesis has been advanced to date which will explain the cause or causes of susceptibility. The knowledge, however, of the chemical properties of the allergen may reveal the nature of the linkage between it and the tissue cells, which gives rise to clinical sensitization. Likewise, the loss of the combining power of tissue cells with the allergen may unfold the mechanism of the loss of susceptibility which occasionally occurs.

The identification and classification of vitamins and the synthesis of some of them have solved many of the problems of nutrition. This fact should lend encouragement to the biochemical attack upon the allergic disturbances from foods. When allergens are available in purified form, future investigators will be in a more strategic position not only to subject theories of the past to crucial test but also to formulate new concepts.

According to time-honored practice, a patient who reacts positively with the cottonseed allergen is enjoined from partaking of all cottonseed products. Cottonseed flour may be used as an adjuvant to wheat flour in the preparation of certain bakery products, pastries and confections. Far more extensive use, however, has been made of cottonseed oil. The oil has found wide application both in commercial and domestic food products. Invariably, the cottonseed-sensitive patient is denied the use of refined cottonseed oil, margarine and plastic shortening made from it, which are the most frequently encountered edible derivatives of cottonseed.

The earlier statements made by Bauman and Walzer portray the limited knowledge of the time, and invite review. Their assertion, "The active principle in cottonseed is probably a protein," may well be modified to read, "The active components of cottonseed include at least two proteins, viz., CS-1 and CS-2." Moreover, a positive cutaneous or intracutaneous reaction with an extract of cottonseed is no indication of sensitiveness to the oil of cottonseed.

In our study,[8] patients highly sensitive to the cottonseed allergen, CS-1A, gave negative reactions to the refined, edible cottonseed oil on contact with the skin, on ingestion and on instillation into the conjunctival sac and upper respiratory tract. Quantities of cottonseed oil dispensed to five patients were, respectively: 100, 150, 200, 500 and 500 ml. In addition, three patients were given saltine crackers spread with a heaping tablespoonful of the hydrogenated cottonseed oil. One patient was provided with a one-pound can of the hydrogenated oil, which was used liberally as a substitute for butter. No ill effects were noted. Finally, eight normal individuals received a single sensitizing injection of a cottonseed serum in a skin site on the upper arm. Six of the eight skin areas exhibited no detectable response following ingestion of cottonseed oil,

but reacted positively to the orally administered cottonseed allergen derived from the seed itself. The remaining two sites were negative.

Likewise, the absence from the oil of the potent allergen of the castor bean has been noted in two case reports. In one very sensitive case[9] the handling of a "castorine" grease, made from solidified castor and other oils, had no injurious effect on the skin or mucous membranes. In the other case[45] the ingestion of castor oil provoked only the therapeutic reaction. The latter patient was employed in a commercial enterprise which utilized castor bean pomace. He was subject to hay fever and asthma, and gave a positive intracutaneous response to a castor bean solution in the dilution of 1 :5,000,000.

It must not be overlooked that primary edible oils are derived from a large number of oil-bearing seeds and that essentially similar processes are employed in the extraction of the oils. Until further evidence concerning allergic sensitiveness to refined oils and fats becomes available, there is seemingly no justification for the dietary restrictions imposed upon allergic patients. Ample evidence has been cited to prove that the specific and exceedingly potent water-soluble allergens of the cottonseed embryo do not occur in refined cottonseed oil. This fact must not be misinterpreted, however, as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered. Rappaport[44] insists that he must be included in the group of patients who are sensitive to cottonseed oil. He adds, moreover, that with some discomfort he could differentiate, subjectively of course, cottonseed oil from corn oil.

Swineford's assertion that there is not a single authentic case of cottonseed oil sensitivity recorded in the literature is, indeed, challenging.

Figley,[21] in collaboration with Stevens, has presented interesting and conclusive details concerning two authentic cases of specific sensitiveness to cottonseed oil. In one, ingestion of the oil gave rise to asthmatic symptoms; in the other, gastrointestinal symptoms. Both patients reacted negatively to cutaneous tests with cottonseed oil, cottonseed meal and highly purified allergen preparation. Examination of the blood in both cases failed to demonstrate reagins for cottonseed allergens. Specific sensitiveness to refined cottonseed oil was demonstrated by oral administration of two dram doses from a series of vegetable oils, the identity of which was unknown either by the patient or the observers at the time of the tests. The presence of cottonseed oil in the samples of vegetable oils was correctly identified on the basis of patients' clinical response—asthmatic seizures in one and abdominal cramps and diarrhea in the other. Stevens' summary of the foregoing study of cottonseed oil sensitiveness is now quoted because it is as instructive as it is appropriate:

"Clinical sensitiveness to ingested edible cottonseed oil was demonstrated under conditions which precluded possible influence of suggestion or anticipation on the part of either patient or observers. Four samples of edible vegetable oils, iden-

tified only by numbers, were administered in two 2- or 3-dram doses to a patient whose history implied, but did not prove, allergic sensitiveness to cottonseed oil. The patient was not sensitive to the protein allergens of the seed kernel. Therefore, this case, though clinically sensitive to ingested cottonseed oil, showed no correlation between clinical sensitiveness to the potent protein allergens of the cottonseed embryo and unidentified allergen present in the refined oil from the seed embryo.

"The time interval between ingestion of cottonseed oil and the onset of allergic symptoms of response was more than twenty minutes. By contrast, the allergic response to ingestion of the protein allergens of cottonseed begins to appear within a few minutes after the ingestant reaches the stomach. Presumably, the water-soluble protein allergens are absorbed by rapid diffusion through mucous membranes and into capillaries of the stomach prior to digestion. The delayed appearance of symptoms from ingestion of a provocative dose of cottonseed oil suggests that the allergen of the oil becomes available only after some degree of digestion, i.e., enzymatic hydrolysis of the fat (triglycerides)." Moreover, the discharge of the stomach contents into the duodenum is retarded by the presence of fats.

The creation of allergic phenomena by nonnitrogenous substances, as exemplified in the cases of cottonseed oil sensitiveness, brings into focus the mechanism involved therein. Recently, Bronfenbrenner[13] has reviewed the extensive literature dealing with the role played by chemical and physical agents in allergy. The allergic reaction is regarded as cellular rather than humoral in character. Accordingly, the conjugation *in vivo* of the antigenic factor with the constituents of exposed tissues may prove an acceptable explanation. This may be applicable to the exceptional individuals who are affected by fats and oils.

The availability of an active and specific fraction of cottonseed has facilitated the study of its absorption and possible excretion. Milk as the vehicle for allergenic substances has claimed the attention of many investigators. Thus, the transmission of sensitizing allergens by breast milk has been regarded as the prelude to sensitization in the infant. It has been shown that the normal intestinal mucosa is permeable to food proteins. Accordingly, ready passage is provided for proteins by means of the circulation to the mammary glands. It has also been alleged that an ingested allergen in the diet of the nursing mother may, therefore, provoke symptoms in the infant. Similarly, milk from cows, fed in part on cereals, flaxseed and cottonseed, is believed to have caused allergic reactions in those persons sensitive to the respective allergens. Milk, on the one hand, is an indispensable article of food for the young and old; on the other hand, milk may initiate and perpetuate the state of allergy. A critical analysis of the evidence, both clinical and experimental, is demanded by this apparent paradox.

Balyeat[4] reported the case of a child who was allergic to wheat. This child gave an eczematous response to cow's milk, only when the animals had been fed with bran. Milk from cows, fed on green fodder, produced no reaction. In contrast, milk from cows fed on peanut hay

produced attacks of asthma in a child, sensitive to peanuts, as related by Black.[11] Huber[34] encountered a patient in his practice "who could not take milk unless the milk came from the farm where no meal was used."

"Occasionally" warned Urbach,[63] "the physician will have to pay attention to the foods eaten by the mother and possibly reaching the child by way of the breast milk." In evidence, several cases of eczema in breast-fed infants had been recorded by Shannon.[47] He attributed the skin condition to specific foods in the mother's dietary. Lyon[39] described a case of extensive angioneurotic edema in an infant, three weeks old, which resulted from beans and corn, eaten by the mother. A striking parallel was offered by Talbot,[61] that of a nursing infant who developed a severe eczema whenever the mother partook of chocolate.

These isolated cases, of which only a few have just been cited, wherein symptoms have resulted from the ingestion of milk-borne allergens, of either human or animal origin, represent but a very small percentage of the total number of allergic infants and children. In all such cases, multiple sensitization is the rule and not the exception. Accordingly, more than one cause may be operative at a given time, and the fallacy of *"post hoc, propter hoc"* reasoning may sway correct judgment. Moreover, the necessity for adequately controlled clinical observations is only too obvious, and reluctance to repeat any procedure which may provoke distressing symptoms is understandable. The burden of proof, nevertheless, rests upon those who maintain that unaltered, undigested protein absorbed from the intestinal canal passes intact into the milk of the mother or of the cow, and that articles in the diet of the nursing mother may prove as potent an allergen as any food given to the infant. The alternative is to demonstrate by approved methods the presence in the milk of the allergen, be it wheat, cottonseed, flaxseed or egg.

The first attempt for such experimental demonstration was made as early as 1923 by Hermann.[29] In his report, the following statement appears: "Cow's milk can and often does contain ragweed pollen protein in sufficient amounts to cause attacks of hay fever by its ingestion." If this assertion is correct, such cow's milk may also act as a sensitizing agent for individuals who drink copiously of milk. Moreover, cows in their bucolic habitat may, likewise, acquire sensitization to the ragweed both by inhalation and ingestion. To determine the presence of ragweed pollen protein in milk, three guinea pigs were sensitized with ragweed antigen by Hermann and later received an intrathecal injection of 0.25 c.c. of milk. This milk was obtained from cows which were fed with ragweed tops. The guinea pigs died of shock. Two normal guinea pigs, used as controls, were unaffected by the intrathecal inocculation of the same milk.

For more accurate judgment of this very important question, a larger series of animals than the three used in the experiment is required.

Moreover, the intravenous administration of the shocking dose would have been preferable to the intrathecal. The controls were inadequate. Normal milk should have been used in the shocking injection of some of the sensitized animals as well as ragweed antigen. It was of primary importance to prove that the method used in sensitizing the guinea pigs with ragweed antigen was satisfactory.

Seven years later, 1930, Donnally[21] described experiments to prove that egg white fed to nursing women was demonstrable in their breast milk. Sites in recipients were sensitized with serum from an egg-sensitive case, and the sensitized sites were tested with the breast milk. His conclusion reads:

"The concentrated whey of breast milk, obtained after raw egg ingestion on an empty stomach and without other food, from three of eight women gave the specific reaction for egg white greater than the control in sensitized sites in two normal recipients for each whey. Four recipients were utilized for the tests"

It is noteworthy that of the eight women, subjected to the experimental feeding with egg, only three (37.5 per cent) yielded positive results. In evaluating results, mathematical values were assigned to the degree of redness and of wheaking at the sensitized sites after injection with the concentrated whey. The difference in the calculated values of the experimental and control sites determined a positive or negative reading. Since the personal equation is inescapable, the reading of the reactions should better have been made by one or more disinterested observers.

The same criticism is applicable to the work of Brunner and Baron.[14] In 1943, these authors studied the problem of ingested protein in human milk. They followed the procedure of Donnally and substituted cottonseed protein for raw egg. Twenty-four nursing women were used in the test. In their summary, they state:

"By means of the passive transfer technique, the presence of cottonseed antigen was definitely demonstrated in the breast milk of seven mothers of the twenty-four studied In five the results were doubtful, in twelve they were negative."

An analysis of their Table II reveals that only one case was strongly positive, six slightly positive, five doubtfully positive and twelve negative. Numerical values in their readings were also employed. The readings of the reactions as unknowns by a disinterested third party may have resulted differently. Nevertheless, one specimen of milk from a total of twenty-four specimens (4.1 per cent) gave a strongly positive reaction. If we accept seven as the number of positive cases, one strongly positive and six slightly positive, the percentage of positive reactors equals 29.1 as compared with 37.5 of positive findings in Donnally's series.

I join Smyth and Bain,[49] and Stuart[58] in dissent from the conclusions drawn by the foregoing investigators on the evidence submitted. In a

preliminary study which I performed in 1942, the results were not in accord with those of Brunner and Baron. Additional criteria were regarded as essential in determining the presence or absence of cottonseed allergen in breast milk. It may not be amiss to present a summary of the investigation.

In the first stage, cottonseed meal was fed in small doses in capsule form to fifteen lactating women on a fasting stomach. Each capsule contained 0.42 gm. of the meal. The minimum number of capsules ingested was ten. The maximum was fifteen. The feeding was continued for six to eight days. A specimen of milk was obtained before feeding. A second specimen was obtained at the end of the feeding period. Two facts were established:

1. Cottonseed allergen could not be demonstrated in the milk by direct testing on cottonseed-sensitive patients, by indirect testing, nor by the use of animals sensitized against cottonseed.
2. Sensitized sites in the recipients were not exhausted by the amount of cottonseed meal ingested.

A change in technique was indicated. It was deemed advisable to administer one large dose of allergenic substance on a fasting stomach.

In the second stage, two test subjects each ingested 100 gm. and 90 gm. of cottonseed meal, respectively; and to each of five test subjects, 1 gm. of the cottonseed allergen, CS-1A, dissolved in 50 c.c. of warm water, was also administered.

The steps in the experiment were as follows:

1. The selection of nonsensitive cottonseed subjects, with negative Wassermann reactions.
2. The sensitization of available recipients with a cottonseed serum for subsequent indirect testing.
3. The securing of specimens of breast milk under aseptic conditions before the feeding of allergenic material.
4. The securing of a specimen of breast milk, after feeding, when the sensitized sites on the test subject reached the stage of maximum intensity.
5. The securing of other specimens of breast milk at times corresponding to the nursing periods.
6. The sensitization of skin sites on the babies of the test subjects with 0.05 c.c. of cottonseed serum.
7. The testing for exhaustion of the sensitized skin sites of the test subjects.
8. The testing of available sensitized skin sites of recipients with the milk specimens.

(The milk was subjected to a long centrifugalization. The fat and corpuscular elements were removed, and the liquid residue was used in intracutaneous testing. It is noteworthy that the milk was not subjected to Seitz filtration.)

9. The testing of milk specimens in sensitized guinea pigs.

On two occasions, the milk specimens were returned from the laboratory as unknowns for testing. In one of the milk series, cottonseed

extract was added to a portion of the milk and served as a positive control, though unknown to us at the beginning of the experiment.

In all the cases, the presence of the cottonseed allergens was neither demonstrable by the passive transfer technique nor by the use of sensitized guinea pigs. The sensitized sites on babies of the test subjects, also, failed to react after nursing.

The necessity for the employment of diagnostic methods other than the injection of sensitized sites with milk readily became evident. The difference in the reactivity of the many skin sites, both the sensitized and nonsensitized, of recipients was, indeed, striking. The injection of breast milk laden with a complexity of organic and inorganic substances into a skin site, previously traumatized by the injection of serum, inevitably gives rise to erythema and nodulation. We can readily understand the readings, slightly positive and doubtfully positive, of Brunner and Baron in their observations, and the difficulty of an accurate evaluation.

In two of the cases, specimens of blood were collected both before and after ingestion of one gram of CS-1A. The two sera collected before ingestion reacted negatively on sensitized sites. One serum collected after ingestion gave weakly positive reactions in three out of four skin sites. The other serum gave a weakly positive reaction in one out of four. It was significant that the sensitized sites of the lactating women were not exhausted after the feeding of one gram of the potent fraction, CS-1A. The sites were tested with a solution of CS-13A in a dilution of 1:10.[6] The question, therefore, arises whether or not the allergen is destroyed in greater part in the stomach or whether there is interference with its total passage through the stomach wall into the circulation.

Spies and his co-workers,[57] in 1945, described a method for the quantitative estimation of the quantities of allergen absorbed from the gastrointestinal tract when CS-1A and defatted cottonseed were ingested. The procedure involves two tests. First, the quantity of CS-1A, introduced intramuscularly, is determined which will react on a site, sensitized with serum from a cottonseed-sensitive subject, and also the amount required to neutralize the reagins in the same site. Second, the quantity of ingested CS-1A or cottonseed is determined which will incite a positive reaction and later neutralize reagins in a sensitized site. By the above method, reactions in passively sensitized sites provide means of comparing the quantities of allergens that enter the circulation as a result of intramuscular injection and absorption from the gastrointestinal tract. Two of their conclusions are noteworthy:

1. Ten micrograms of CS-1A introduced intramuscularly were approximately equivalent to 100,000y of ingested CS-1A in capacity to incite passive-transfer reactions. On this basis, when 100 mg. of CS-1A were ingested, 0.01 per cent of the allergenic fraction was absorbed.

2. One hundred micrograms of CS-1A introduced intramuscularly were approximately equivalent to 800,000y of ingested CS-1A in reagin-neutralizing power. According to this criterion, when 800 mg. of CS-1A were ingested, 0.013 per cent of the allergenic fraction was absorbed.

It becomes apparent that quantitatively a very small amount, 0.01 to 0.013 per cent, of an ingested allergen from the cottonseed is absorbed into the circulation and disseminated throughout the body to reach potential shock organs. Its fate in the mammary gland can no longer be in doubt. The mammary gland is a factory to which raw materials are conveyed. The resulting product, milk, differs chemically and physically from other body fluids. Allergens may accordingly be incorporated into the finished product or be rejected and passed on to the organs of excretion. However, many drugs ingested by a nursing mother may appear in her breast milk. Rosenau[40] furnishes the following list of drugs which have been found in such milk: aspirin, iodine, mercury, arsenius acid, potassium bromide, and probably also hexamethylenamine, salicylic acid and salicylates, ether, antipyrine, bromides, caffeine and many others. It is possible that the size or weight of the molecule of the circulating substance, be it derived from drug or food ingested, determines its passage through the cells of the mammary gland into the milk.

The consensus is that the larger the molecule, the less is the likelihood of its passage through the cellular linings. Interestingly enough, the active allergenic protein components of CS-1A pass through a cellophane membrane which is virtually impervious to egg albumin in the same system.

It must now be emphasized that nonallergic subjects have been used, by necessity, in the studies which have been made on the possible excretion of allergens in human milk. Moreover, the conclusions which have been drawn from those studies have been applied to allergic mothers. It is well to recall that allergy has been defined by Von Pirquet, in 1907, as a state of altered reactivity. The reactions of the allergic individual to certain stimuli differ from those of the normal to the same stimuli; and the same differences must exist between allergic and nonallergic mothers. Is the assumption, therefore, warranted that a nursing mother, sensitive to cottonseed, would transmit the potent allergen to her suckling infant after the ingestion of cottonseed meal, either by accident or design?

Nevertheless, certain articles of food in the mother's diet have been held responsible for acute exacerbations of skin and catarrhal conditions in their nursing babies. No one to date has conclusively demonstrated the presence of such offending allergens in human milk.

Expectant mothers and nursing mothers are warned of the dangers of overindulgence lest their offspring become sensitized and yet they are advised to increase their food intake to meet their added requirements. Thus, in a recent article Roberts[45] attempts to explain how the child becomes allergic: first, through food—overindulgence of cravings

or excessive eating on the part of the expectant mother; secondly, by transmission of antibodies from the mother by way of breast milk.

A more extended study of milk-borne allergens, if any, is surely indicated. The time is now at hand for students of physiology and of allergy to co-operate. In an attempt to solve some of the problems, I have sought in vain for many years for acute cases of hay fever or pollen asthma in actively lactating women. The determination of the presence or absence of an inhalant allergen in the breast milk of nursing mothers during their seasonal period of symptoms would confirm or contradict prevailing concepts.

The genesis of allergy is still an open question. The recent scholarly dissertation by Abramson[2] on "Psychodynamics and the Allergic Patient" adds a mental factor to the physical and chemical factors in etiology. Psychic trauma, it has been suggested, plays an important role.

We are now living in an age unparalleled in human history, and mass experiments have been unwittingly carried on. In the Old World, as the result of a devastating war, physical and psychic trauma, malnutrition and starvation have left an imprint on the survivors. In the Far East, the effects upon the genes by irradiations from atomic explosions will be disclosed by a new generation.

Twenty years hence, when the rising generation shall have reached maturity, the medical historian will then have the rare opportunity to compare and contrast the state of allergy in the New World with that of the Old. Moreover, the "contrarities" of allergic manifestations may then be successfully linked with the subtleties of the chemical structure of allergens.

REFERENCES

1. Abramson, H. A.; Moore, D. H.; Gettner, H.; Gagarin, J., and Jennings, L.: Electrophoretic isolation of constituents of ragweed pollen extracts. J. Am. Chem. Soc., 62:1627, 1940.
2. Abramson, H. A.: Psychodynamics and the Allergic Patient. St. Paul: Bruce Publishing Company, 1948.
3. Alilare, E.: Etudes sur la ricine. Hypersensibilite a la ricine. Am. Inst. Pasteur, 28:605, 1914.
4. Balyeat, R. M.: Allergic Eczema. J. Allergy, 1:516, 1930.
5. Bauman, L.; Chudnoff, M., and Mackenzie, G. M.: Attempts to separate the active constituents of ragweed pollen. Proc. Soc. Exper. Biol. & Med., 11:226-227, 1924.
6. Bernton, H. S.; Jones, D. B., and Csonka, F. A.: Pollen proteins and their clinical significance in hay fever. A preliminary communication. South. M. J., 20:257-264, (April) 1927.
7. Bernton, H. S.; Spies, J. R., and Stevens, H.: Evidence of the multiplicity of allergens and reagins in cottonseed sensitiveness. J. Allergy, 13:289, 1942.
8. Bernton, H. S.; Spies, J. R., and Stevens, H.: Significance of cottonseed sensitiveness. J. Allergy, 11:138, 1940.
9. Bernton, H. S.: Castor bean sensitiveness. Case report with discussion of principles. J. South. M. A., 38:670, 1945.
10. Black, J. H.: A soluble specific carbohydrate of ragweed pollen. J. Allergy, 2:161, 1931.
11. Black, J. H.: Quoted by Balyeat, R. M.: Acquisition of specific hypersensitiveness. South. M. J., 21:554, 1928.
12. Blackley, C. H.: Hay Fever: Its Causes, Treatment and Effective Prevention. 2nd ed. London: Baillière, Tindall & Cox. 1880.

13. Bronfenbrenner, J.: Is the hypersensitiveness to chemical and physical agents allergic in nature? J. Allergy, 14:105, 1943.
14. Brunner, M., and Baron, B.: The presence of ingested cottonseed protein in woman's milk. J. Allergy, 13:358, 1942.
15. Caulfield, A. H. W.: Skin tests on hay fever cases with chemically different fractions from ragweed pollen. Proc. Soc. Exper. Biol. & Med., 23:14-16, 1925-26.
16. Caulfield, A. H. W.; Cohen, A., and Eadie, G. S.: The antigenic properties of pollen fractions. J. Immunol., 12:153-175, (Aug.) 1926.
17. Caulfield, A. H. W: Prausnitz-Kustner reaction with sera of ragweed hay fever patients to ragweed carbohydrate fraction. Proc. Soc. Exper. Biol. & Med., 31:573, 1934.
18. Caulfield, A. H. W.; Brown, M. H., and Waters, E. T.: Experiments to determine whether the allergically active substance in ragweed pollen extract is a single entity or multiple. J. Allergy, 7:1, 1935.
19. Coca, A. F.; Walzer, M., and Thommen, A. A.: Asthma and hay fever in theory and practice. P. 394. Baltimore: Charles C. Thomas, 1931.
20. Csonka, F. A.; Bernton, H. S., and Jones, D. B.: Proteins of timothy and orchard grass pollen and their relation to vernal hay fever. Proc. Soc. Exper. Biol. & Med., 13:14-16, 1925.
21. Donnally, H. H.: The question of the elimination of foreign protein (egg white) in woman's milk. J. Immunol., 19:15, 1930.
22. Dunbar, W. P.: Zur Ursache und specifischen Heilung des Heufiebers. Munchen: R. Oldenbourg. 1903.
23. Feinberg, S. M., and Aries, P. L.: Asthma from food odors. J.A.M.A., 98: 2280, 1932.
24. Figley, K. D.: Cottonseed oil sensitivity. Letters Int. Corres. Club Allergy, 5:30, 1942.
25. Grove, E. F., and Coca, A. F.: The nature of the pollen atopen. Proc. Soc. Exper. Biol. & Med., 21:48, 1923.
26. Harley, D.: Hay fever. The skin reactive potency of protein and carbohydrate fractions of timothy pollen. British J. Exper. Path., 18:469, 1937.
27. Hecht, R.; Rappaport, B. Z., and Welker, W. H.: Studies on the chemistry and immunology of ragweed pollen proteins. Proc. Soc. Exper. Biol. & Med., 39:588, 1938.
28. Heidelberger, M., and Avery, O. T.: The soluble specific substance of pneumococcus. J. Exper. Med., 38:73, 1923.
29. Hermann, E. T.: Milk transmission of pollen hay fever. Minnesota Med., 6:159, 1923.
30. Heyl, F. W.: Analysis of ragweed pollen. J. Am. Chem. Soc., 39:1470, 1917.
31. Heyl, F. W.: The protein extract of ragweed pollen. J. Am. Chem. Soc., 41: 670-682, 1919.
32. Horesh, A. J.: Allergy to food odors. Its relation to the management of infantile eczema. J. Allergy, 14:335, 1943.
33. Horesh, A. J.: Allergy to odor of white potato (Irish potato). J. Allergy, 15:147, 1944.
34. Huber, H.: Discussion of reference.[14]
35. Johnson, C. A., and Rappaport, B. Z.: The proteins of ragweed pollens. J. Infect. Dis., 50:290, 1932.
36. Jones, D. B., and Csonka, F. A.: Proteins of the cottonseed. J. Biol. Chem., 64:673, 1925.
37. Kammann, O.: Zur Kenntnis des Roggen-pollens und des darin enthaltenen Heufiebergiftes, beitrage zur chemischen Physiologie und Pathologie. Band, 5:346-354, 1904.
38. Lippard, V. W., and Schmidt, W. M.: Human passive transfer antibody. Am. J. Dis. Child., 54:288, 1937.
39. Lyon, G. N.: Allergy in an infant of three weeks. Am. J. Dis. Child., 36:1012, 1928.
40. Metzger, F. C.: Personal communication.
41. Moore, M. B.; Cronwell, H. W., and Moore, E. E.: Studies on pollen and pollen extracts. V. Skin reactions to pollen extracts. J. Allergy, 2:85, 1930.
42. Newell, J. M.: A review of chemical studies on the allergens in pollens. J. Allergy, 13:177, 1942.
43. Prausnitz, C., and Kustner, H.: Studien uber die Ueberempfindlichkeit. Centralbl. fur Bakteriol., 86:160, 1921.
44. Rappaport, B. Z.: Discussion of reference 8.
45. Roberts, W. G.: Protecting your child from allergy. Hygeia, p. 602, (Aug.) 1947.

46. Rosenau, M. J.: Preventive medicine and hygiene. 6th ed. New York: D. Appleton Century Co., 1935.
47. Shannon, W. R.: Eczema in breast-fed infants as a result of sensitization to foods in the mother's dietary. Am. J. Dis. Child., 23:392, 1922.
48. Service, W. C.: Antigenic studies of polysaccharides isolated from pollen. Colorado Med., 34:468, 1937.
49. Smyth, F. C., and Bain, K.: Enteral absorption of the antigen and the apparent failure of antigen secretion in human milk. J. Allergy, 2:282, 1931.
50. Spain, W. C.: Food hypersensitiveness. New York State J. Med., 33:100, 1933.
51. Spies, J. R.; Bernton, H. S., and Stevens, H.: The chemistry of allergens. I. Isolation of an active fraction from cottonseed. J. Allergy, 10:113, 1939.
52. Spies, J. R.; Coulson, E. J.; Bernton, H. S., and Stevens, H.: The chemistry of allergens. II. Isolation and properties of an active protein component of cottonseed. J. Am. Chem. Soc., 62:1420, 1940.
53. Spies, J. R.; Bernton, H. S., and Stevens, H.: The chemistry of allergens. III. The solubility behavior of an active protein picrate from cottonseed. J. Am. Chem. Soc., 62:2793, 1940.
54. Spies, J. R.; Chambers, D. C.; Bernton, H. S., and Stevens, H.: The chemistry of allergens. VII. The nature of the unidentified allergens of cottonseed. J. Allergy, 14:7, 1942.
55. Spies, J. R., and Coulson, E. J.: The chemistry of allergens. VIII. Isolation and properties of an active protein-polysaccharidic fraction, CB-1A, from castor beans. J. Am. Chem. Soc., 65:1720, 1943.
56. Spies, J. R.; Coulson, E. J.; Chambers, D. C.; Bernton, H. S., and Stevens, H.: The chemistry of allergens. IX. Isolation and properties of an active, carbohydrate-free protein from castor beans. J. Am. Chem. Soc., 66:748, 1944.
57. Spies, J. R.; Chambers, D. C.; Bernton, H. S., and Stevens, H.: Quantitative estimation of the absorption of an ingested allergen. J. Allergy, 16:267, 1945.
58. Stuart, H. C.: The excretion of foreign protein in human milk. Am. J. Dis. Child., 25:135, 1923.
59. Stull, A.; Sherman, W. B., and Hampton, S. F.: Antigenic fractions in ragweed pollen. I. Water soluble fractions. J. Allergy, 12:117, 1941.
60. Swineford, Jr., O., and Weaver, W. M.: History taking in allergy: An outline for and a comparison of results from 200 histories and skin tests. Ann. Int. Med., 20:293, 1944.
61. Talbot, F. B.: Eczema in childhood. M. Clin. North America, 1:985, 1918.
62. Tuft, L.; Blumstein, G. I., and Wenger, L. J.: Studies in food allergy. IV. Variations in allergenic activity of food extracts. J. Allergy, 16:92, 1945.
63. Urbach, E.: Allergy. P. 834. New York: Grune and Stratton, 1943.
64. Wolff-Eisner, A.: Das Heufieber. Munich: J. F. Lehmann, 1906.

HAROFE HAIVRI, THE HEBREW MEDICAL JOURNAL

With the appearance of Volume 11, 1948, *The Hebrew Medical Journal* edited by Moses Einhorn, M.D., concludes its twenty-first successful year of publication.

In publishing the journal, the editors aim to meet the need for a medical journal written in Hebrew, with English summaries, thus aiding greatly in the advancement and development of Hebrew medical literature.

This issue contains an article on "Hypertensive Vascular Disease" by Benjamin Jablons, M.D. There is also a discussion on clinical observations and treatment of 190 cases of "Malaria in Palestine" by P. Ephrati, M.D., of Tiberias.

In addition, under the heading of "Personalia," biographical sketches of Professor Heinrich Finkelstein, pediatrician; Professor Max Neuburger, medical historian; and Solomon Solis-Cohen, M.D., of Philadelphia, are presented.

For further information, communicate with the Editorial Office of *The Hebrew Medical Journal*, 983 Park Avenue, New York 28, New York.

REPEATED PATCH TESTING IN ALLERGIC ECZEMATOUS SENSITIZATION

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THERE are numerous differences of opinion among the various investigators regarding the stability of the level of hypersensitivity in allergic eczematous contact-type sensitization and regarding the persistence or permanency of such sensitization.

Our own interest in this problem was heightened by an unpublished observation of Sulzberger and Baer. A random group of inmates of a penal institution were patch tested with a poison ivy extract and, from among these, a group of subjects with strongly positive reactions was selected for further study. When several months later this group was retested with the same extract, some of the previously strongly reacting subjects unexpectedly reacted with a decidedly diminished response. It seemed, therefore, that a study on a group of subjects where each patient would be repeatedly patch tested with the same eczematogenic allergen might produce results bearing on the stability of the level of sensitivity.

Among the many interesting theoretical and practical questions involved in a study of this sort, we have been primarily interested in the following:

1. Will the results of successive patch tests be identical when such tests are performed with the same material repeated weekly over a prolonged period and in a standardized manner on a patient with allergic eczematous contact-type hypersensitivity?
2. If the results are not identical, does the repeated application of the eczematogenic agent under a patch show (or produce?) a trend toward increased or decreased sensitivity?*
3. Where the readings with usually employed concentrations of test materials show little or no variation, can a change in sensitivity be demonstrated by the technique of graded dilutions?

The answers to these questions have wide implications. The stability of the level of patch test sensitivity is of obvious importance for the evaluation of the results of patch tests performed once, as done in medical practice as well as in medicolegal and workmen's compensation work. Also, if the changes in sensitivity on repeated patch testing are consistently in the direction of decreased sensitivity, a method for hyposensitization in allergic eczematous contact-type dermatitis might evolve from this procedure.

Wedroff and Dolgoff[17] experimentally sensitized fifty out of seventy-two

These studies were carried out under a fellowship grant for research in dermatologic allergy given by Luzier's, Inc., through The American College of Allergists.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, N. Y. Post-Graduate Medical School and Hospital, Dr. Marion B. Sulzberger, Director.

*It will be noted that all changes in sensitivity were demonstrated by patch testing. Increased sensitivity was demonstrated through more intense reactions and decreased sensitivity through less intense reactions.

eczema patients by the topical application of 2:4 dinitrochlorbenzene. They were able to observe forty-one of the fifty patients from ninety to 360 days. Twenty-eight of the subjects became spontaneously desensitized, and thirteen showed diminished hypersensitivity during the period of observation, as indicated by testing with graded dilutions of the allergen. They noted that in some cases the skin tests temporarily boosted the level of sensitivity.

Sulzberger and Rostenberg[11] retested six subjects previously deliberately sensitized to either or both paranitrosoanilin and 2:4 dinitrochlorbeneze after five to sixteen months. When retested, five of the subjects reacted either to the same degree as earlier or showed increased sensitivity. The remaining subject showed a loss of sensitivity to one of the two eczematogenic agents tested.

Kanof and Rostenberg[6] compared the incidence of sensitivity to poison ivy extract in a group of persons incarcerated in a mental institution and in a group of non-incarcerated controls living in the same community. The incarcerated subjects gave 15.5 per cent positive reactions, whereas the control subjects gave 25 per cent positive reactions. These findings suggested that acquired specific sensitivity of the contact type can persist for many years without exposure to the causative allergen, but that there may be in some persons a tendency for reduction or loss of sensitivity when the sensitized individual is removed from contact with the offending allergen.

In a series of experiments, Field and Sulzberger[2] repeatedly patch tested a subject who had been previously deliberately sensitized to poison ivy. An acetone extract of poison ivy leaves in graded dilutions from 1:1 to 1:1,000,000 was used in this study. They concluded that because of the unpredictable chronological fluctuations as well as the variations of sensitivity in different skin areas, evaluation of variations in response is nearly impossible, unless tests are repeated many times and in different skin areas.

Sulzberger, Kanof, and Baer[12] described a case of hypersensitivity to cinnabar with subsequent reduction or loss of sensitivity which was evident both clinically and by patch test.

Omitting references to the many publications on specific hyposensitization by injection, ingestion, et cetera, the following sets forth some of the pertinent references dealing with attempts at deliberate specific hyposensitization by external applications in allergic eczematous contact-type dermatitis.

Shelmire[10] hyposensitized a young man with a poison ivy dermatitis by repeatedly applying many patch tests with varying dilutions of the allergen. Four other patients, treated in a similar manner, showed only a slight reduction in skin sensitivity.

J. Jadassohn[5] claimed the accomplishment of hyposensitization in a patient with turpentine dermatitis by four external applications of the

allergen using a method similar to patch tests. The article stated that Hoffert was also successful in a few similar cases.

Patch tests with gradually increasing concentrations of neoarsphenamine were used by Riehl[9] for hyposensitization. His case history, however, indicated that the reduction in sensitivity occurred one year after the applications of the allergen.

Maisel[8] treated a patient with poison ivy hypersensitivity using daily baths containing increasing amounts of Rhus Toxicodendron tincture. After the daily baths, the patch test reaction was only slight, and the patient apparently had immunity to clinical re-exposure to poison ivy.

Kesten and Laszlo[7] treated a nurse suffering from an eczematous dermatitis of the hands due to exposure to a 1:5000 solution of potassium mercuric iodide. The hands were immersed daily in gradually increasing concentrations of the chemical, until such a time when scrubbing with the above dilution failed to produce a dermatitis.

Urbach[15] reported successful desensitization to garden sage by external applications of various 2 per cent extracts of the plant.

Biberstein[1] made observations on patients who had been deliberately sensitized to poison ivy. His studies were primarily confined to investigation of changes in local sensitivity without regard for the reaction of the general skin surface. He found that the level of local sensitivity was not always constant, now and then being wave-like. In most cases, the repeated daily applications of the allergen produced local desensitization.

A technique for "epidermal" hyposensitization was described by Urbach and Gottlieb.[16] The technique consists of starting with very high dilutions of the offending allergen applied to the skin on a one-inch square patch of linen or cotton and gradually increasing the concentration of the allergen and the size of the patch. This procedure is continued until a concentration is reached equal to that to which the patient would be ordinarily exposed. The authors do not state the efficacy of this technique in actual practice.

Pertinent animal experiments have been reported by Ginsberg, Stewart, and Becker.[3] Guinea pigs were painted daily with a 5 per cent ether dilution of a ragweed extract until a moderate exudative dermatitis developed. In a few instances the dermatitis underwent complete involution despite continued paintings. The authors considered this result analogous to "hardening."

EXPERIMENT 1—PATCH TESTS AT WEEKLY INTERVALS WITH SINGLE CONCENTRATIONS OF THE ALLERGEN

Technique.—Subjects showing positive reactions on patch tests with *standard* concentrations† of eczematogenic contact-type allergens were selected from among the clinic patients. These subjects were seen twice

†Unless otherwise specified in these experiments, all substances were employed in the usual patch test concentrations as listed in *Office Immunology*, Sulzberger and Baer, Editors, Year Book Publishers, Inc., 1947. These concentrations will, in this paper, be referred to as the *standard* concentrations.

weekly. On the first visit each week they were tested with the allergen or allergens to which they had previously been shown to be hypersensitive. The tests were left in place for forty-eight hours, at the end of which time the reactions were read and recorded according to a modified Bloch classification.* All patch tests were applied and read by the authors. Throughout the experiment every effort was made to maintain standardization of all procedures.

The patches were applied to the upper back in almost all cases, using the right and left sides alternatingly. A deliberate attempt was made to avoid the use of the same exact site for consecutive tests. Approximately the same amount of the allergen was applied each time.

In the case of dyed materials (cloth, leather, et cetera) the same size patch was used for each application (¼-inch square). In the case of liquids, approximately equal amounts were measured by keeping constant, as well as possible, the amount of liquid applied to the pre-cut muslin ¼-inch square patches. In the case of ointments and creams, an amount enough to cover a ¼-inch muslin patch without excess was used for all tests.

Ten subjects were tested with one substance, four subjects with two substances and the remaining four subjects were tested with three, four, five, and six substances, respectively. The shortest period of time for which any subject was followed was four weeks and the longest was thirty-five weeks. An attempt was made to apply the tests once weekly, although this was not always possible. Three substances were tested weekly over a four-week period; two substances for five weeks; three for six weeks; seven for seven weeks; six for eight weeks; one for ten weeks; five for eleven weeks; three for twelve weeks; two for fourteen weeks; two for twenty-six weeks; one for thirty-four weeks; and one substance for thirty-five weeks.

Results.—The results of Experiment 1 are shown in Figure 1†† and are based on the tests in eighteen subjects who were tested with a total of thirty-six substances.

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*Modified classification used:
- 0 No reaction.
- (+) Faint erythema.
- + Definite erythema.
- ++ *Erythema, infiltration* and beginning papule and vesicle formation.
- +++ *Papule* and *vesicle formation*, erythema and infiltration; or bullae.
- ++++ *Large confluent bullae*, erythema and infiltration, or denudation and necrosis.

Original Dr. Bloch classification (*Office Immunology*, page 14):
- 0 No reaction.
- (+) Mildest erythema.
- + Erythema.
- ++ Erythema and edema and/or beginning papulation or vesiculation.
- +++ Fully developed vesiculation, papulation, edema, bullae.
- ++++ Strongest reaction-denudation, necrosis, etc.

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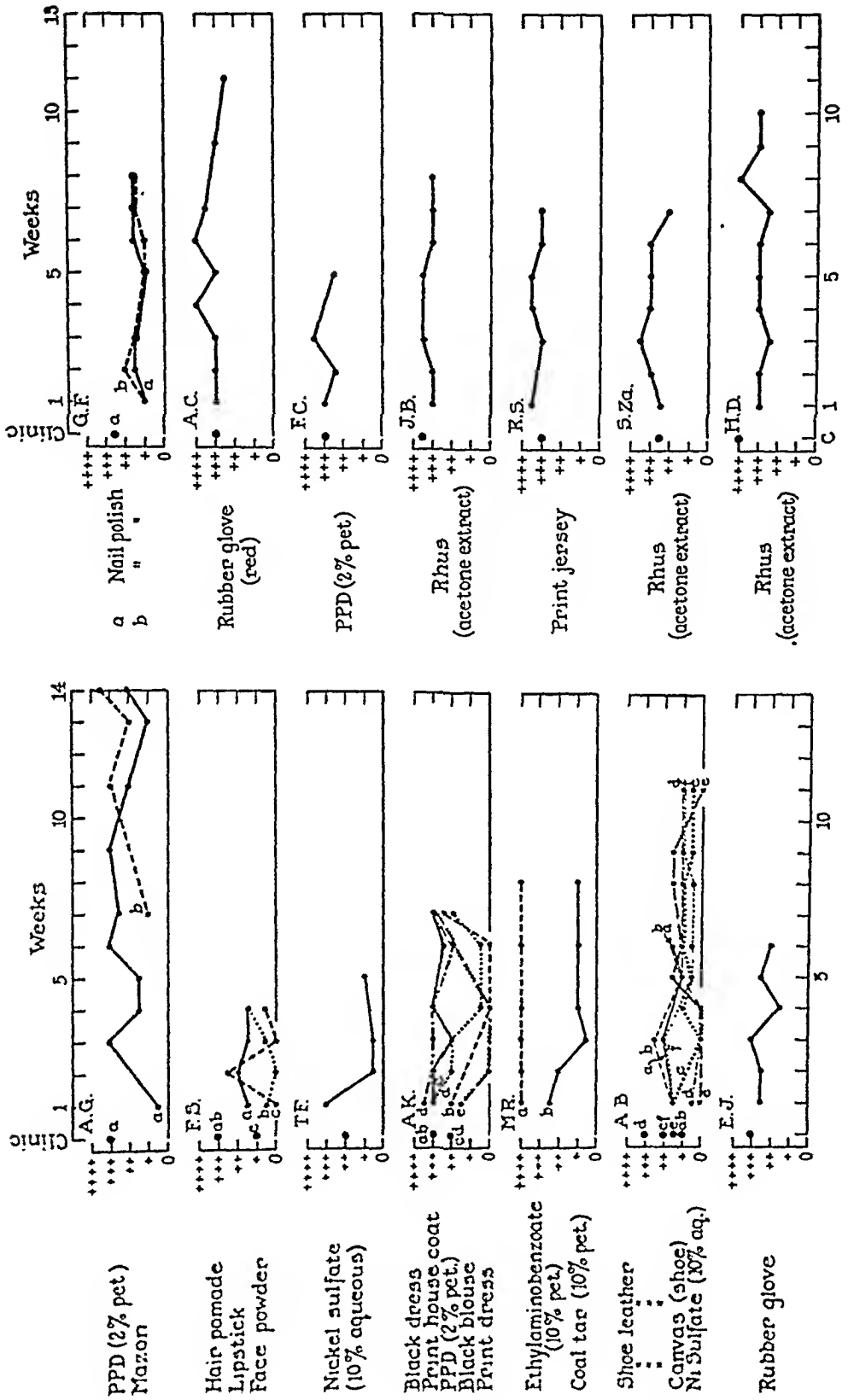
††The initial patch test readings charted under the heading "Clinic" were taken from the clinic charts as read and recorded by a trained technician at the time the patient's hypersensitivity *to patch tests with the particular agent was discovered. These* readings have been included for the sake of completeness. In no instance was the "Clinic" reading included in the evaluation of the patch test responses in the repeated tests, as the technique in these "Clinic" tests, although generally similar to the ones used by the authors, was not necessarily exactly the same as that used in all of the other tests listed. In each patient the interval between the "Clinic" reading and the reading of the first patch test done by the authors varied from one week to several months.


Clinic
Weeks
A.G.
a PPD (2% pet)
b Mazon
F.S.
a Hair pomade
b Lipstick
c Face powder
T.F.
Nickel sulfate (10% aqueous)
A.K.
a Black dress
b Print house coat
c PPD (2% pet.)
d Black blouse
e Print dress
M.R.
a Ethylaminobenzoate (10% pet.)
b Coal tar (10% pet.)
A.B.
a Shoe leather
b " " "
c " " "
d Canvas (shoe)
e Ni Sulfate (10% aq.)
f Rubber glove
E.J.
G.F.
a Nail polish
b " "
A.C.
Rubber glove (red)
F.C.
PPD (2% pet)
J.B.
Rhus (acetone extract)
R.S.
Print jersey
S.Za.
Rhus (acetone extract)
H.D.
Rhus (acetone extract)

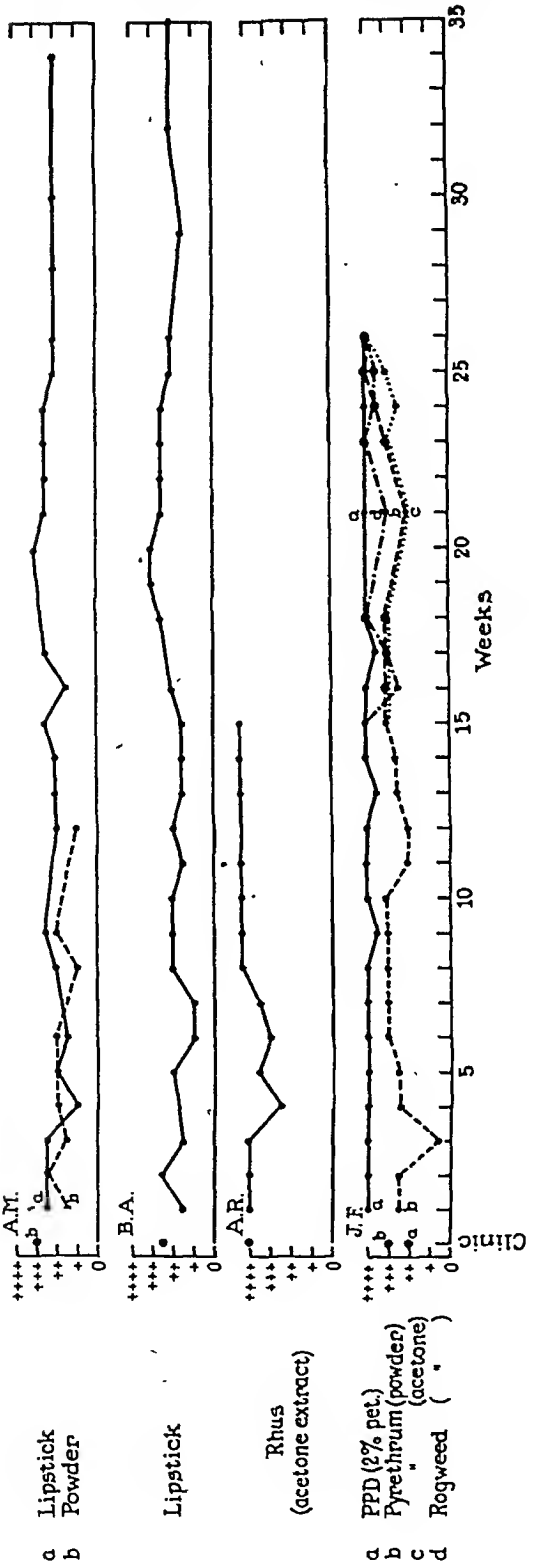


Fig. 1. Patch tests with standard concentrations.

Because of the possibilities for technical error inherent in the technique of patch testing, only variations of *more than 1 plus* in the readings from week to week were considered evidence of increased or decreased sensitivity.

Comparing the results obtained *in the very last patch test* with the results obtained in the *first patch test* (excluding the "Clinic" reading for the reasons previously mentioned), out of the thirty-six substances used there are four instances of increased sensitivity (Case A.G., paraphenylenediamine and Mazon; Case A.K., print dress; and Case J.F., pyrethrum powder); and one instance of decreased sensitivity (Case T.F., nickel sulfate).

Comparing differences in non-consecutive tests, i.e., the *minimal patch test response obtained at any one test* with the *maximal patch test obtained at any one test,* there are variations of more than 1 plus in fifteen patients with a total of twenty-three substances, i.e., with 64 per cent of the substances tested in this series.

Variations of more than 1 plus in *consecutive patch test readings* were found in twelve subjects with a total of sixteen substances, i.e., with 44 per cent of the substances tested in this series.

It is noteworthy that in some of the cases (Cases A.G., A.K., A.B., G.F., and J.F.) which were tested simultaneously with two or more substances, there appeared to be a tendency to parallel increases or decreases in sensitivity to these substances.

EXPERIMENT 2—PATCH TESTS AT WEEKLY INTERVALS WITH GRADED DILUTIONS

Technique.—The same method of selection of patients as well as of application and reading of patch tests described for Experiment 1 was employed in this series of cases. However, instead of repeatedly testing with only a single concentration, the tests were carried out with graded dilutions of the allergens. Dilutions were made in multiples of 10, and testing was done with at least four different dilutions of each substance. Testing was begun by using the allergen in the *standard* concentration and the 1:10, 1:100, and 1:1000 dilutions of this concentration.* When more than two of these dilutions produced a 3 plus or greater reaction, the stronger concentrations were not again employed in the subsequent tests; instead higher dilutions were used, e.g., 1:10,000, 1:100,000 and 1:1,000,000. In this manner an attempt was made to choose the consecutive concentrations so that the weakest concentration would produce no response or a slight response (0 to 1 plus) and the strongest concentration would produce a strong response (3 to 4 plus).

Tests were done in four subjects with paraphenylenediamine, in three subjects with an acetone extract of Rhus Toxicodendron†, in one subject

*The only exception to this rule was with paraphenylenediamine in which the dilutions of the standard concentration of 2 per cent in petrolatum were the following: 1:2; 1:20; 1:200; et cetera.
†Prepared by Graham Laboratories.

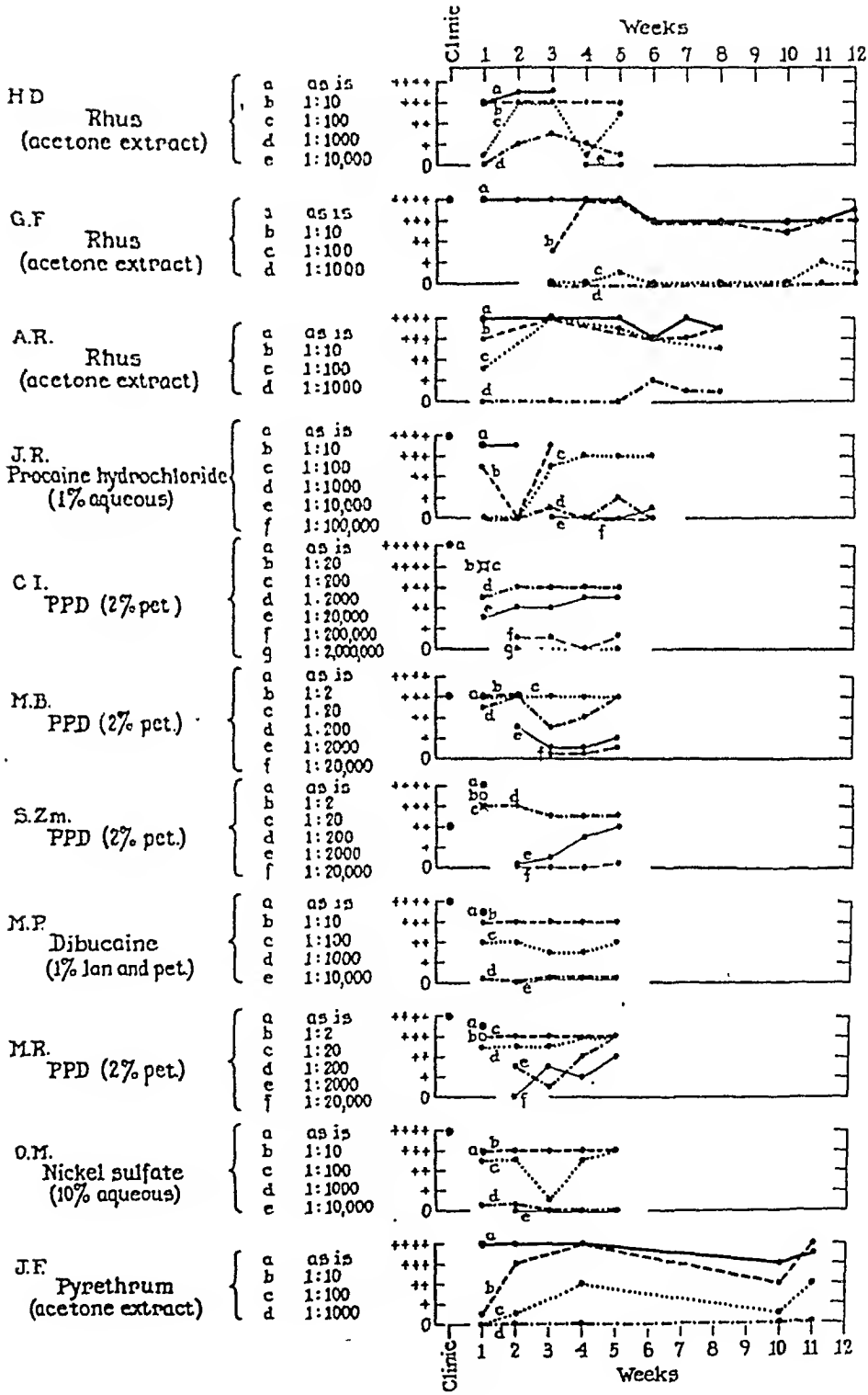


Fig. 2. Patch tests with graded dilutions.

with procaine hydrochloride, in one subject with dibucaine,* in one subject with nickel sulfate, and in one subject with an acetone extract of pyrethrum.†

Results.—The results of Experiment 2 are shown in Figure 2, and are based on the tests in the above eleven subjects, each of whom was tested with dilutions of a single allergen for a minimum of five weeks.

In all of the subjects, the level of skin response remained approximately the same from one week to the next for the strongest test concentration employed.

Comparing the results obtained with the dilutions *in the very last patch test* with the results obtained *in the first patch test,* out of the eleven subjects there are six who showed increased sensitivity (Case H.D., Rhus Toxicodendron 1:100; Case G.F., Rhus Toxicodendron 1:10; Case J.R., procaine hydrochloride 1:100; Case S.Zm., paraphenylenediamine 1:2000; Case M.R., paraphenylenediamine 1:2000 and 1:20,000; and Case J.F., pyrethrum 1:10 and 1:1000). There were no instances of decreased sensitivity.

Comparing the differences in non-consecutive tests, i.e., the *minimal patch test response obtained with the dilutions of any one test* with the *maximal patch test response obtained at any one test,* there are variations of more than 1 plus in eight patients with a total of twelve dilutions, i.e., with 27 per cent of the forty-four dilutions in this series, which were tested more than two consecutive times.

Variations of more than 1 plus *in consecutive patch test readings* were found in seven subjects with a total of ten dilutions, i.e., with 23 per cent of the forty-four dilutions in this series.

Again as in Experiment 1, it is noteworthy that in some of the cases (Cases G.F., A.R., C.I., M.B., M.P., and J.F.), there was a tendency to parallel increase or decrease in sensitivity to two or more dilutions.

EXPERIMENT 3—PATCH TESTS AFTER VARIOUS TIME INTERVALS

Technique.—In this experiment those patients who returned after various intervals of time following the last patch tests performed in Experiments 1 and 2 were retested. The same substances or dilutions in the same concentrations as last employed on the patient were again used in each instance. One case was retested after an interval of six weeks, three after seven weeks, one after nine weeks, one after twenty-one weeks, one after twenty-four weeks, and one after an interval of eight months.

Results.—The results of Experiment 3 are shown in Figure 3 and are based on the tests in these eight subjects.

The same level of sensitivity as noted in the last previous tests was maintained in the majority of instances, i.e., with twenty-four out of twenty-nine substances or dilutions. In four patients, there were five

*Supplied by [illegible]
†Prepared by [illegible]

instances of variations in sensitivity greater than 1 plus. These variations occurred only with the weaker concentrations of the graded dilutions. They are as follows:

In patient G.F., retested after twenty-four weeks, there was an increased sensitivity to the 1:100 dilution of the standard concentration of

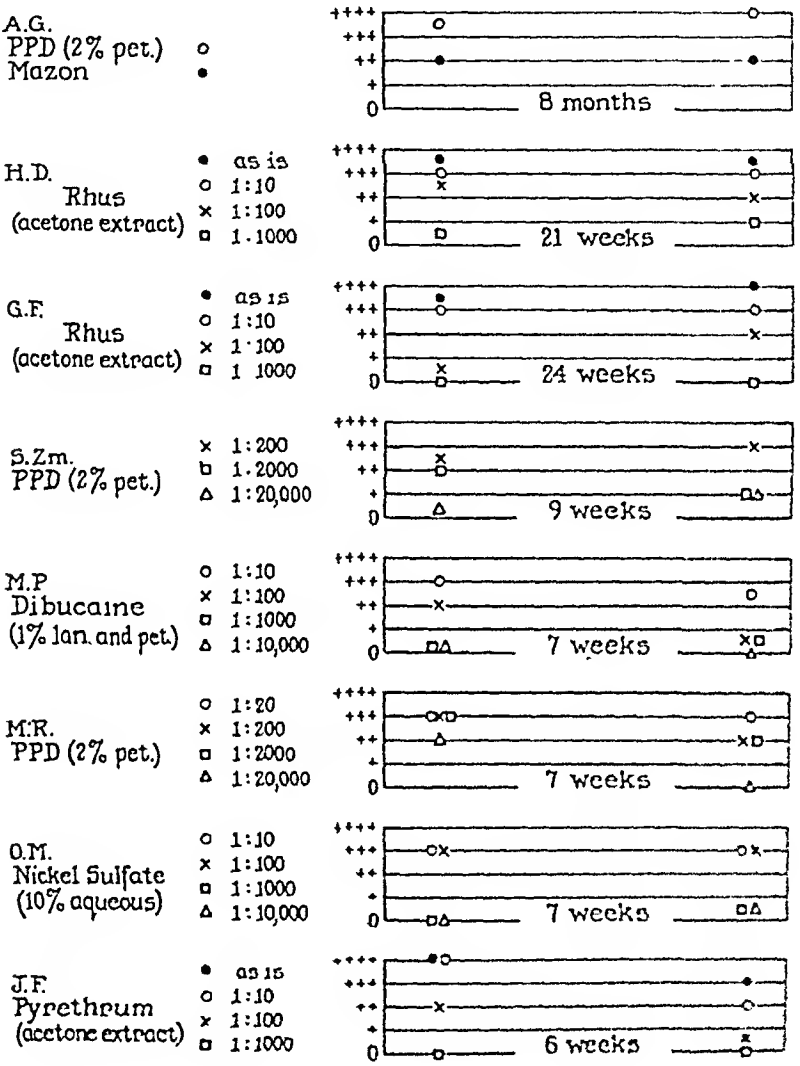


FIG. 3. Patch tests after various time intervals

Rhus Toxicodendron. The patient denied having had any [illegible] exposure to or any contact with poison ivy during the interval between [illegible] There was no change in the responses to the [illegible] 1:10 and 1:1,000 dilutions.

In patient M.P., retested after seven weeks, the [illegible]

sensitivity to the 1:100 dilution of the standard concentration of dibucaine. The responses to the 1:10, 1:1,000 and 1:10,000 dilutions showed no change.

Patient M.R., retested after seven weeks, showed a decrease in sensitivity to the 1:20,000 dilution of the standard concentration of paraphenylenediamine. The responses to the 1:20, 1:200, and 1:2,000 dilutions showed no change.

In patient J.F., the reactions to the *standard* concentration, the 1:10 and 1:100 dilutions of pyrethrum extract all followed the same trend toward decreased sensitivity. It is interesting to note that in this patient patch tests carried out one week later showed that the sensitivities to the various concentrations had reverted to their previous levels (Fig. 2).

COMMENT

Our studies indicate that when a patch test is repeated weekly over a prolonged period of time and in a standardized manner consecutive readings are not always identical. Variations of more than 1 plus occurred for a substantial number of the substances or dilutions tested, i.e., with 44 per cent in Experiment 1 and with 23 per cent in Experiment 2. When non-consecutive readings are considered, the incidence of variations of more than 1 plus is even higher, i.e., with 64 per cent in Experiment 1 and 27 per cent in Experiment 2. Despite the changes in sensitivity just mentioned, the repeated application of *standard* concentrations of eczematogenic agents did not in general show a trend toward prolonged or permanent increase or decrease in the level of sensitivity of the skin during an average period of observation of three months. When the last patch test reading was compared with the first, of the thirty-six substances tested in Experiment 1, four showed an increased level and only one a decreased level of sensitivity.

Though no variation in the level of sensitivity was demonstrable in most cases in Experiment 1 where patch tests with *standard* concentrations were employed, changes in the level of sensitivity may have occurred which were not detected by this method. This is suggested by the results of patch tests with graded dilutions in Experiment 2, where six of the eleven patients tested with dilutions at weekly intervals showed some evidence of an increase in hypersensitivity, while none of these subjects showed a persistent trend to increased hypersensitivity in the tests with the strongest concentrations employed.

Our observations demonstrate that patch tests performed with *standard* concentrations of an allergen can be expected to show the existence of skin hypersensitivity of slight, moderate, or strong degree, but are not suitable to demonstrate relatively small variations in the level of sensitivity. The fact that the *standard* or similarly strong concentrations of an allergen, when used for patch testing, serve only as a "rough" indicator of sensitivity is evidenced by the concomitant application of *graded dilutions* of the

same allergen. Whereas strong concentrations caused reactions of approximately the same degree with repeated patch tests, some of the graded dilutions brought to light definite and distinct variations from one test to the next. In all instances where such variations occurred, they were in the direction of increased hypersensitivity.

Furthermore our results show that the weekly repetition of patch tests is not a procedure suitable for hyposensitizing patients to eczematogenic allergens. The results, however, do not necessarily negate the findings of other authors who have reported successful hyposensitization using topical applications of eczematogenic allergens. Among the differences between the experimental conditions existing in the studies of other investigators and our own are that they often used (1) different allergens, (2) larger quantities of the allergens covering larger body areas, (3) application of the allergens over longer periods, (4) more frequent applications of the allergens and, (5) application of gradually increasing concentrations of the allergens.

Where tests were performed simultaneously with two or more allergens, there were a few instances in which the curves followed a similar pattern of increased or decreased sensitivity. This indicates that the level of skin sensitivity sometimes shows a nearly corresponding trend towards increased or decreased sensitivity to all of the allergenic substances coming in contact with it at any one particular time. It is not possible to decide whether these variations occurred despite or because of the repeated applications of the allergens.

No conclusions can be drawn from our experiments concerning the controversial questions of "hardening" caused by continued or repeated exposures to an eczematogenic allergen. The condition of exposure of persons who are said to have developed "hardening" were not duplicated in our studies.

In Experiment 3, when patients were retested after intervals of time varying from six weeks to eight months, it was found that the same level of sensitivity had been maintained for the majority of substances or dilutions, i.e., for twenty-four of the twenty-nine tested. There was one instance of increased sensitivity and four instances of decreased sensitivity in this experiment, all of which were demonstrable only with graded dilutions.

The decreased level of sensitivity which could be demonstrated with dilution tests in these subjects, after intervals presumably without exposure to the allergen, fits in with the findings of Wedroff and Dolgoff and Kanof and Rostenberg.

On the other hand, the results of Sulzberger and Rostenberg indicate that in many persons the level of hypersensitivity is maintained unchanged over long periods of time, although occasionally spontaneous desensitization apparently occurs.

Our studies also tend to show, in keeping with previous investigators,

that repeated periodic exposures to a specific allergen tend to increase rather than decrease the level of hypersensitivity.

The question arises whether the variations in the patch test results described by us may have occurred due to factors other than actual changes in the level of hypersensitivity to the allergens. The margin of error of the patch test method as such may have played a role in producing these results. Local differences in sensitivity between the site used for the test with a given material during one week and the site used for testing with the same material at a later date must also be considered. This would be in keeping with the observations that a high level of sensitivity often exists adjacent to the affected or previously affected areas in allergic eczematous contact-type dermatitis,[7,13,14] or with differences in skin sensitivity, as noted by Hoffert[4] between normal skin areas and areas in which the skin is under tension. Moreover, variations in the skin response may also have resulted from unsuspected clinical exposure to the allergen during the experiment.

It is not likely that these factors account for all of the changes in level of hypersensitivity observed by us. The simultaneous increases or decreases in skin hypersensitivity to two or more substances of dilutions tested, as well as the trend toward increased hypersensitivity which occurred with weaker dilutions of an allergen while at the same time stronger dilutions repeatedly gave identical reactions, would be hard to explain on the basis of the factors just mentioned, i.e., the technical errors inherent in this method of testing, the local differences and variations in sensitivity, and the possibility of unsuspected clinical exposure to the allergens.

SUMMARY AND CONCLUSIONS

Patch tests were performed in a standardized manner repeatedly over many weeks on subjects who were known to be hypersensitive to one or more eczematogenic allergens. These tests were done with the *standard* concentrations, i.e., those usually used for patch testing, as well as with *graded dilutions* of these concentrations.

Patch tests repeatedly performed at weekly intervals with *standard* concentrations of allergens did not always give identical results; yet they were sufficiently consistent to indicate that the standard patch test procedure is a highly reliable method of testing for allergic eczematous contact-type hypersensitivity. This method of testing can be depended upon to show slight, moderate, or strong degrees of hypersensitivity.

Graded dilutions of an allergen on repeated patch testing did show variations in levels of sensitivity which were not shown by the *standard* concentrations. Therefore tests with graded dilutions of an allergen are more satisfactory for demonstrating relatively small variations in sensitivity than are tests with standard concentrations.

Our experiments indicate that if there is any change in the level of hypersensitivity as produced by repeated patch tests, it is not in the direc-

tion of decreased sensitivity, demonstrating that the method of repeated weekly applications of an allergen under a patch as done under our experimental conditions is not satisfactory for effecting desensitization in allergic eczematous contact-type hypersensitivity.

REFERENCES

1. Biberstein, H.: Über Hautreaktionen bei Applikation von Verschiedenen Rhusarten. Klin Wchschr., 8:1, 1929.
2. Field, H., and Sulzberger, M. B.: Experiments in poison ivy sensitivity. J. Allergy, 7:139, 1936.
3. Ginsberg, J. E.; Stewart, C. D., and Becker, S. W.: Cutaneous sensitization studies. J. Invest. Dermat., 2:81, 1939.
4. Hoffert, E.: über fixes Quecksilber-Exanthem und durch Hautspannung Bedingte Quecksilber—überempfindlichkeit. Arch. F. Dermat. und Syph., 147:135, 1924.
5. Jadassohn, J.: Bemerkungen zur Sensibilisierung und Desensibilisierung bei den Ekzemen. Klin. Wchschr., 2:1734, 1923.
6. Kanof, N. M., and Rostenberg, A., Jr.: Observations on persistence of sensitivity of eczematous type after prolonged periods of removal from contact with the allergen. J. Invest. Dermat., 4:175, 1941.
7. Kesten, B., and Laszlo, E.: Dermatitis due to sensitization to contact substances. Arch. Dermat. and Syph., 23:221, 1931.
8. Maisel, F.: Poison ivy. A new method of immunization. J. Allergy, 4:35, 1932.
9. Riehl, G.: Zur Frage der Allergeschen Hauterkrankungen Praktische Auswertung der Allergieforschung. Arch. f. Dermat. und Syph., 157:57, 1929.
10. Shelmire, B.: The poison ivy plant and its oleoresins. J. Invest. Dermat., 4:337, 1941.
11. Sulzberger, M. B., and Rostenberg, A., Jr.: Acquired specific supersensitivity (allergy) to simple chemicals. J. Immunol., 36:17, 1939.
12. Sulzberger, M. B.; Kanof, A., and Baer, R. L.: Complications following tattooing, sensitization and desensitization to mercury; report of a case. U. S. Naval M. Bull., 43:889, 1944.
13. Sulzberger, M. B.; Baer, R. L., and Kanof, A.: Clinical uses of 2,3-dimercaptopropanol (BAL). V. Skin sensitization to BAL. J. Clin. Investigation, 25:488, 1946.
14. Sulzberger, M. B.; Kanof, A.; Baer, R. L., and Lowenberg, C.: Sensitization by topical application of sulfonamides. J. Allergy, 18:92, 1947.
15. Urbach, E.: Experimentelle Studien zur Frage der Perkutanen Desensibilisierung. Zentralbl. f. Haut und Geschl. Krkh., 44:507, 1933.
16. Urbach, E., and Gottlieb, P. M.: Allergy, Second Ed. New York: Grune and Stratton, 1946.
17. Wedroff, N. S., and Dolgoff, A. P.: über die spezifische Sensibilität der Haut einfachen chemischen Stoffen gegenüber. Arch. f. Dermat. und Syph., 171:647, 1935.

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HISTAMINE-SYMPATHIN BALANCE

FRANCISCO J. FARRERONS-CO, M.D., F.A.C.A.
Barcelona, Spain

IN the course of investigations initiated in collaboration with Prof. Dr. Jimenez-Vargas, Staub's research on the behavior of histamine of the adrenergic type was confirmed. Initial tests suggested the possibility that Sympathin in the presence of histamine behaved in a way very similar to that of epinephrine. We have continued and developed further these experiments.

The similarity of epinephrine and Sympathin led us to study the behavior of histamine under the action of Sympathin. There was some doubt as to this similarity in the previous research of Cannon and Rosenblueth, but it was afterwards proven by Euler, after numerous and careful experiments, that Sympathin is not the same as epinephrine and that its pharmacological behavior is nearer to, or perhaps identical with 1-Nor-epinephrine or Catecol-Etanol-Amine.

After some preliminary tests, comparison of the action of Sympathin and of epinephrine on the vasomotor reaction of the ergotaminized cat led to the same conclusions as those of Euler, that Sympathin is not like epinephrine, but is an organic product with characteristics similar to epinephrine being nearer, as the above mentioned author has said, to 1-Nor-epinephrine.

TECHNIQUE OF EXTRACTION

For the extraction of the Sympathin we followed the standard procedure proposed by Euler in his various publications. Some of these were described and confirmed by him in personal correspondence.

A part of the organ (we used the spleen and heart of calves; liver, heart and spleen of dogs) removed from a recently killed animal was ground and placed in two parts of alcohol of 96°, to which was added 1 c.c. of 10 normal H_2SO_4 per liter. The extraction takes about two hours, after which it is filtered and evaporated in a vacuum, reducing the volume of the extract to about a tenth of the original. It is then treated with ether to extract the fats, and this extract, which can be called "crude extract," is then ready for the tests. This extract was employed in the majority of our experiments.

This crude extract, which contains appreciable quantities of Sympathin, contains also organic substances of a cholinic type. This can be observed after injection into experimental animals, by decrease of the arterial pressure, compensated later on by the action of the Sympathin.

This depressor factor of the crude extract can be eliminated by later purification, founded on the fact that Sympathin is insoluble in ether but

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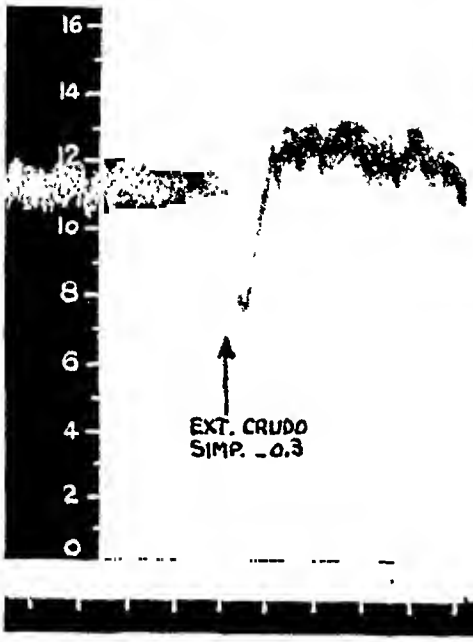


Fig. 1. Effect on the blood pressure of the cat from injection of 0.3 c.c. of crude Sympathin extract. Observe descent of pressure after injection of the extract, followed by a marked hypertensive effect.

Fig. 2. Behavior of the cat's blood pressure under the effect of injection of 0.25 c.c. of extract of Sympathin-ether-lipoids.

soluble in a solution of ether-lipoids, whether of a lecithin type or extracted from the brains. For this purpose 1 volume of the crude extract is treated with 2 volumes of ether-lecithin* at 5 per cent, separating this layer of ether which then contains the Sympathin.

This, in its turn, is extracted from the ether solution, due to its solubility in water, with a solution of sodium sulphate at 5 per cent. For this, about 10 per cent of the volume of crude Sympathin is used. This operation is repeated three times and the volume collected is then treated with 3 volumes of Ethanol to precipitate the salts. It is filtered and evaporated in alcohol. This extract still contains certain quantities of depressor substance which are finally eliminated with Almeria earth ("Fuller's earth") although certain loss of Sympathin is effected in this operation.

For a concentration of the extract of 1.5 gr. of organ per c.c. adjusted to a pH 4, the extract is treated carefully with the Almeria earth with a tenth part of the volume of a suspension of earth in water at 20 per cent. This treatment must be repeated often.

*The ether-lecithin solution was kindly supplied by the Wassermann Laboratory in Barcelona.

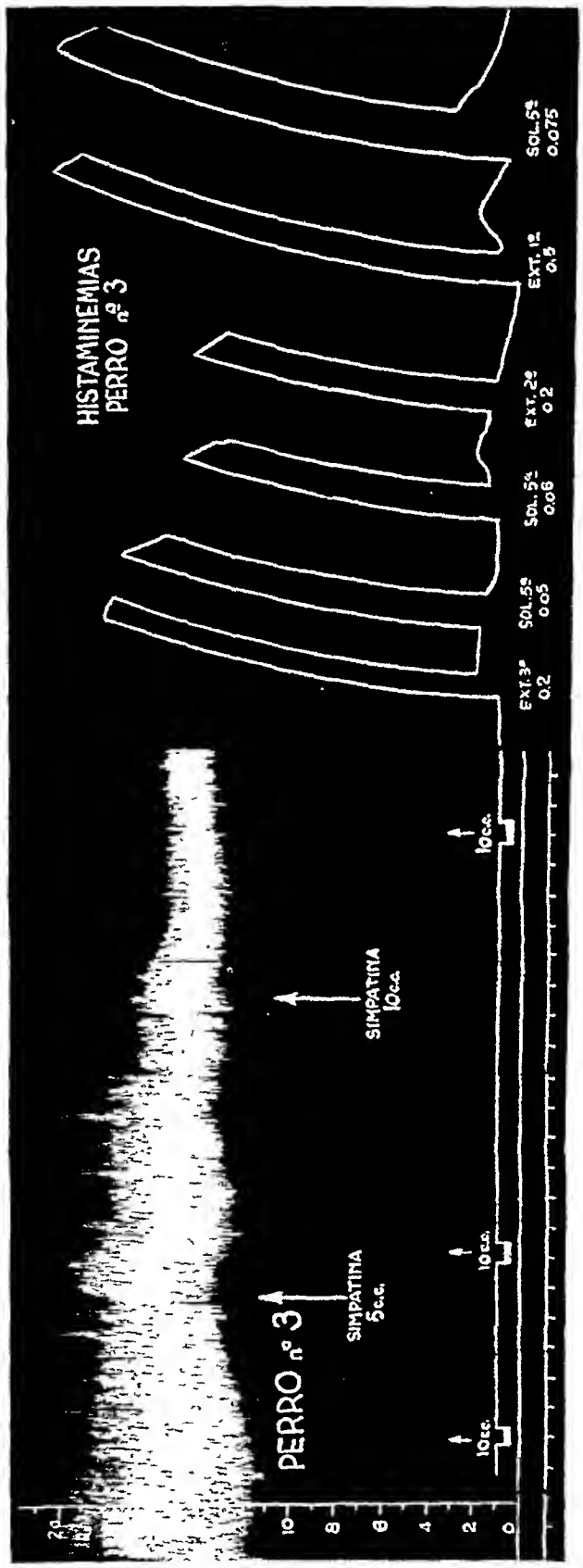


Fig. 3. Effect of Sympathin extract on a dog.

TABLE I. HISTAMINE VALUES IN DOGS BEFORE AND AFTER THE INJECTIONS OF SYMPATHIN

Number of Animal	Injected Sympathin	Histamine	
		Before	After
2	5 c.c.	0.75 γ %	.2 γ %
2 bis	10 c.c.	0.75 γ %	1.2 γ %
3	5 c.c.	0.15 γ %	0.30%–0.30 γ %
4	5 c.c.	2. γ %	4.5 γ %
5	5 c.c.	0.8 γ %	0.8 γ %
6	4 c.c.	0.35 γ %	0.4 γ %
7	4 c.c.	0.04 γ %	0.05 γ %
8	5 c.c.	0.025 γ %	0.2 γ %

DEMONSTRATION

Demonstration is done by intravenous injection in the anesthetized cat, provided with an adequate cannula in the carotid artery to record arterial pressure.

Before beginning the experiment, and in order to make vasomotor reactions of the animal more sensitive, 8 mg. of cocaine per kg. are injected intravenously, and 1/10 mg. of ergotamine per kg. is injected intramuscularly.

When the extract appears to possess appreciable hypertensor properties, it is then utilized for basic experiments (Figs. 1 and 2).

REGULATION OF HISTAMINE-SYMPATHIN

Action of Histamine in the Dog in the Presence of Sympathin.—In seven dogs, previously anesthetized with dial and provided with cannulas in the carotid artery to register their blood pressure, a quantitative determination of histamine was made, the amounts of which are given in Table I. "Crude extract" was then injected into the dogs in the saphenous vein, in quantities varying between 4 to 10 c.c. as per details in Table I.

In all of the dogs the extract has shown obvious pressure properties, an example of which is shown in Figure 3.

At the maximum of its blood pressure, we again extracted blood from the dog for a new determination of histamine,† the values of which are also given in Table I.

In all of these dogs, each of which was subjected to eight tests, it was observed that parallel with the increase of arterial pressure, the quantity of histamine likewise increased.

As a control we used a number of dogs into which an extract without Sympathin was injected, an extract which was on the contrary very high in depressor substances, due to the extract having been prepared using the same technique and procedure mentioned previously, but many hours after the death of the donor animal. As an example we may use dog No. 1 (Fig. 4). A determination of histamine before injecting the extract and another at the moment of minimum pressure proved that, parallel with the

†The technique employed in the determination of histamine has been that of Code.

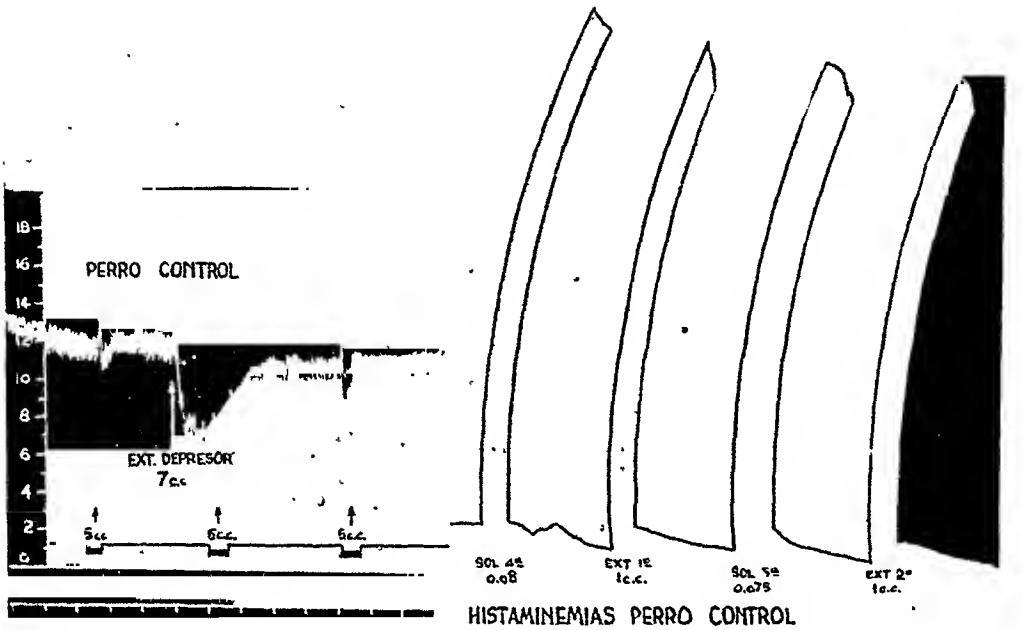


Fig. 4. Effect of extract containing depressor substances instead of Sympathin.

fall of arterial pressure, the histamine contents diminished in appreciable quantities (Table II).

The summary of these experiments on these groups of dogs, calculated in medium values, is represented correlatively in Figures 5 and 6.

TABLE II. CONTROL DOGS INJECTED WITH EXTRACT WITHOUT SYMPATHIN

Number of Animal	Quantity Injected	Histamine	
		Before	After
1	7	1.6 γ %	0.15–1.6 γ %

Histamine-Sympathin "in situ" (Loop of Guinea Pig).—Another group of experiments was made to study the behavior of Sympathin in the intestinal loop of a guinea pig, contracted by histamine.

An intestinal loop of a guinea pig (end portion of the ileum), of 4.5 cm. in length, is submerged in a bath of tyrode at 37°-38°. One gamma of chlorhydrate of histamine is added, with the object of provoking the well-known contracting action. Under these conditions; known and varied quantities of crude extract of Sympathin fluctuate between 0.2 of a c.c. and 0.4 of a c.c. In all the cases, and after a first reactional ascent due to the increase of contraction of the loop, because of the depressor factor contained in the extract, a notable and visible descent of the curve can be observed in consequence of the relaxation of the loop. Once at this stage of relaxation, new and repeated quantities of histamine are introduced, similar to those which had before produced the contraction of the loop (0.1 gamma

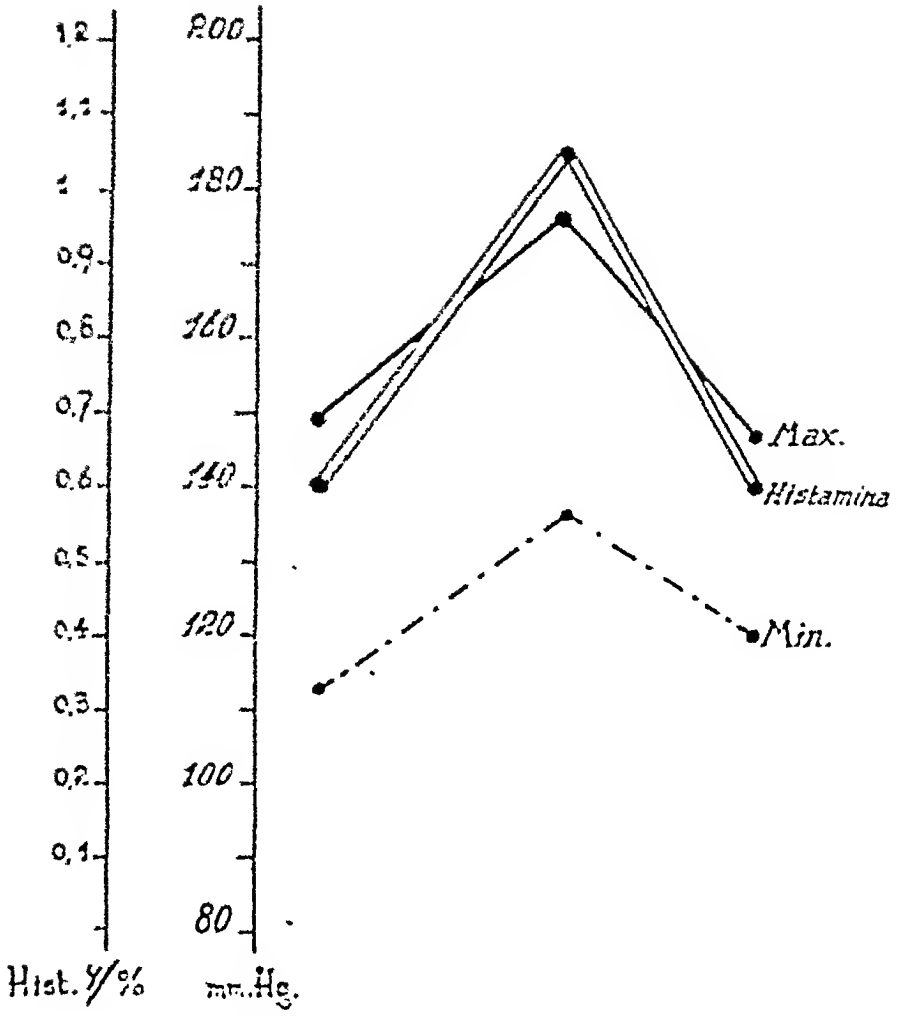


Fig. 5. Average values of blood pressure and histamine in eight tests.

of histamine), and no contraction is observed. Later introductions into the bath of quantities of histamine, ten and even a hundred times greater than the initial ones, do not produce any contraction of the loop either. The behavior of acetylcholine present in the loop relaxed by Sympathin has also been investigated. The introduction of 1 gamma, 10 gammas or 1 mg. of acetylcholine produces no modification whatever in said loop (Fig. 7).

ANTIHISTAMINIC ACTION OF SYMPATHIN I:

In this second type of experiments, and given the similarity already mentioned between epinephrine and Sympathin, we studied the antihistaminic effect of Sympathin. For this purpose, we carried out three different types of experiments.

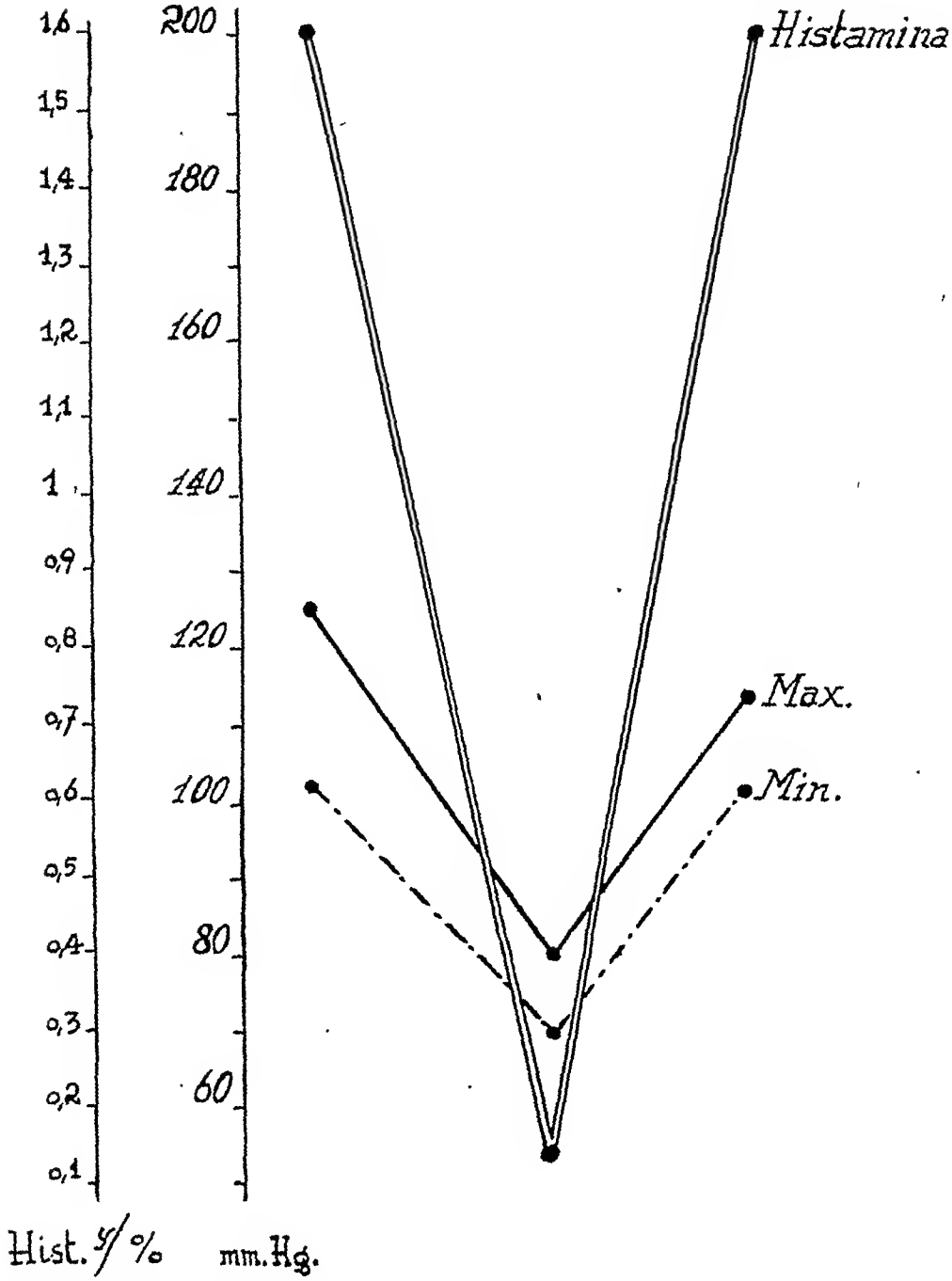


Fig. 6. Average values of blood pressure and histamine in a control dog injected with a depressor extract.

Action of Sympathin Present in a Lethal Dose of Histamine

This experiment was performed in both guinea pigs and rabbits.

Results in Guinea Pigs.—We experimented on four different groups of guinea pigs with no distinction in the groupings, other than that they were all injected with Sympathin of the same origin (Sympathin extracted from one and the same organ and on the same date for each group).

TABLE III. ANTIHISTAMINIC ACTIVITY OF SYMPATHIN IN THE PRESENCE OF LETHAL DOSES OF HISTAMINE IN DIVERS SERIES OF GUINEA PIGS

	1 No.	2 Weight	3 Sympathin Injected	4 Histamine Injected	5 Shock
Group A:	1	360	0.35 c.c	0.21 c.c.	No
1 Guinea Pigs	2	305	0.3	0.18	No
	3	650	0.63	0.15	No
	4	280	0.28	0.15	No
Group B	1	410	0.41	0.24	No
	2	475	0.47	0.28	Yes
	3	350	0.35	0.21	No
	4	290	0.29	0.17	Yes
	5	330	0.33	0.19	No
Group C:	1	520	0.52	0.31	Yes
	2	620	0.62	0.37	No
	3	370	0.37–1 c.c.	0.22	Yes
Group D:	1	265	0.26–1 c.c.	0.15	Yes
	2	275	0.27–1 c.c.	0.16	No
	3	290	0.29–1 c.c.	0.17	Yes

2nd column: Weight of animal.
3rd column: Quantities of Sympathin injected. Way of adm[illegible]
4th column: Chlorhydrate histamine (mg.) injected correspon[illegible] 0.6 mg. for every 1 g. as lethal dose. Way of [illegible]
5th column: Resisted shock.
Died of shock.

Before administering the lethal dose of histamine, each group was treated preventatively with a dose of the extract varying between 0.28 c.c. and 1.37 c.c. (These latter doses proved to be excessive, as the autopsy and pathological examination showed that death was due to this excessive dose of Sympathin and not to histamine) (Figs. 8, 9, 10 and 11).

The detailed results obtained in this group of experiments are shown in Table III. From it, it may be observed that six guinea pigs died under the effects of histamine but nine survived it, a proportion of 60 per cent. The quantity of 0.6 mg. per kg. in weight was considered as a lethal dose for these animals.

Results in Rabbits.—The results in these animals were, as may be seen in Table IV, much more significant, due, possibly, to the greater technical facilities for the introduction of both the Sympathin and the histamine.

As in the experiment with the guinea pigs, the rabbits were likewise divided into three groups. In the first of these that received insufficient quantities of Sympathin, none of the three rabbits injected with a lethal dose of histamine survived.

Rabbit No. 1 of the second group, which received an excessive quantity of Sympathin, died under the effects of same, as was verified by the autopsy and the pathological report (Figs. 12, 13, 14 and 15). The rest of the rabbits of this second group, as well as the ten rabbits of the third and last group which received adequate doses of Sympathin, survived the histaminic shock, with the exception of one which died and another which had a moderate histaminic shock and died fifteen minutes later.

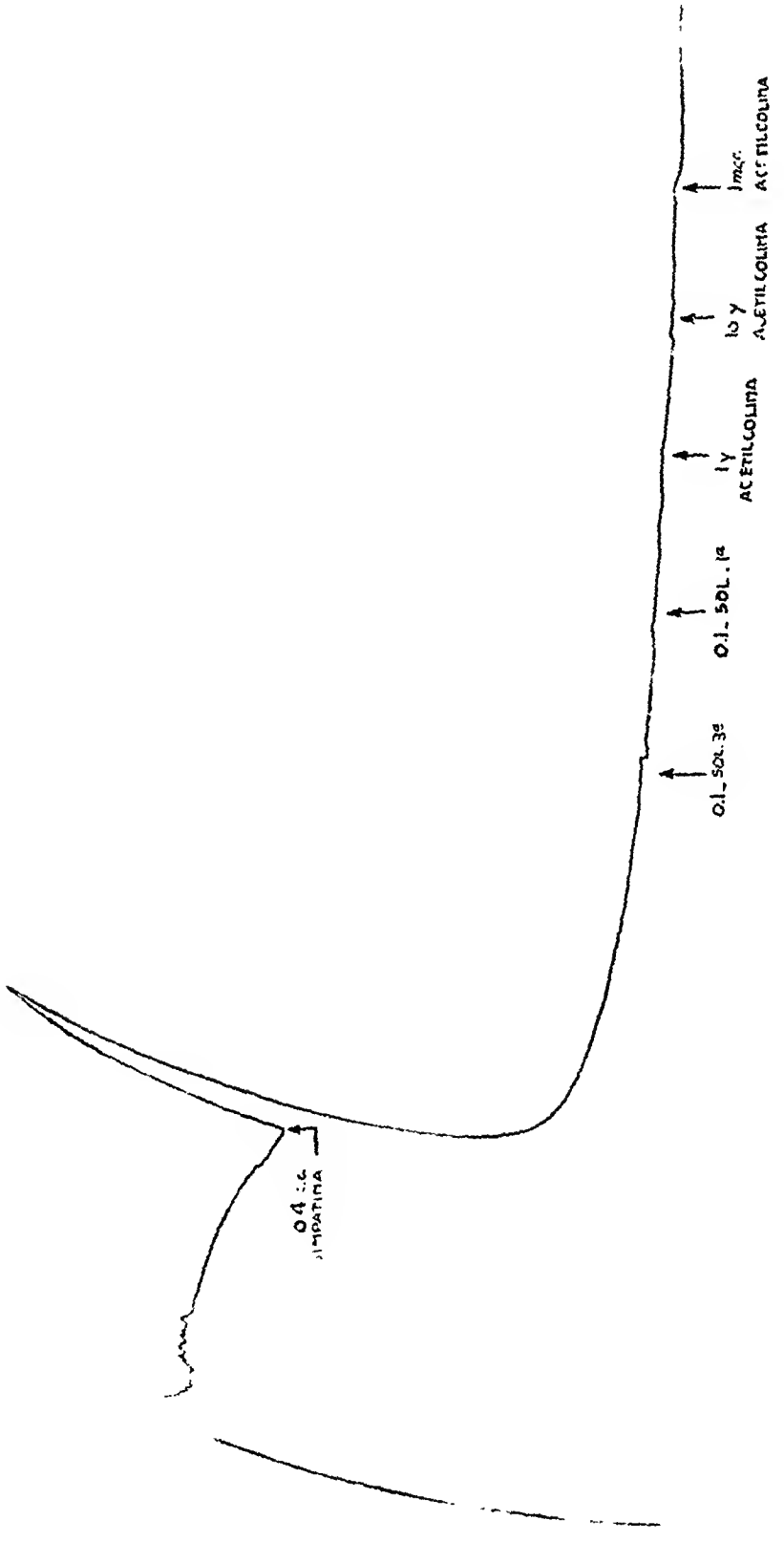


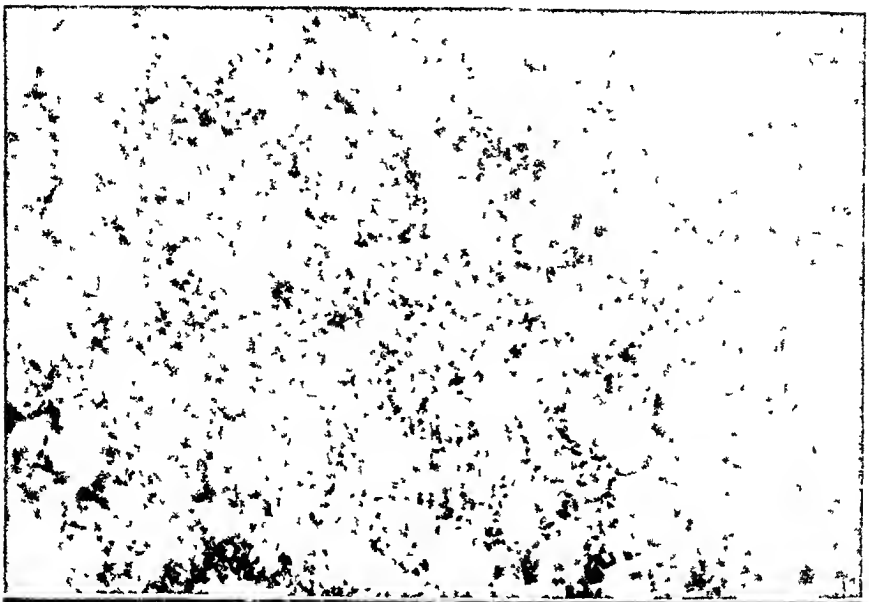
Fig. 7. Relaxation with Sympathin of a guinea pig's loop, contracted with histamine. New additions of histamine do not contract it; neither does an addition of acetylcholine. The ascent observed by the introduction of crude Sympathin extract corresponds to the cholinergic and depressive substances found in same.

Fig 8. Aspect of the heart and lungs of a guinea pig which died of lethal doses of Sympathin. Observe the pronounced cardiac dilatation and atelectatic and hemorrhagic lungs.

Fig. 9. Aspect of the heart of a guinea pig which died of anaphylactic shock. Emphysema and characteristic dilatation of the lungs are present

Fig. 12. Aspect of the heart of a rabbit which died from a heavy dose of Sympathin (Sympathin shock). Observe the rather characteristic lesion of the burst heart.

Fig. 13. Aspect of the heart and lungs of a rabbit which died of a lethal dose of histamine.



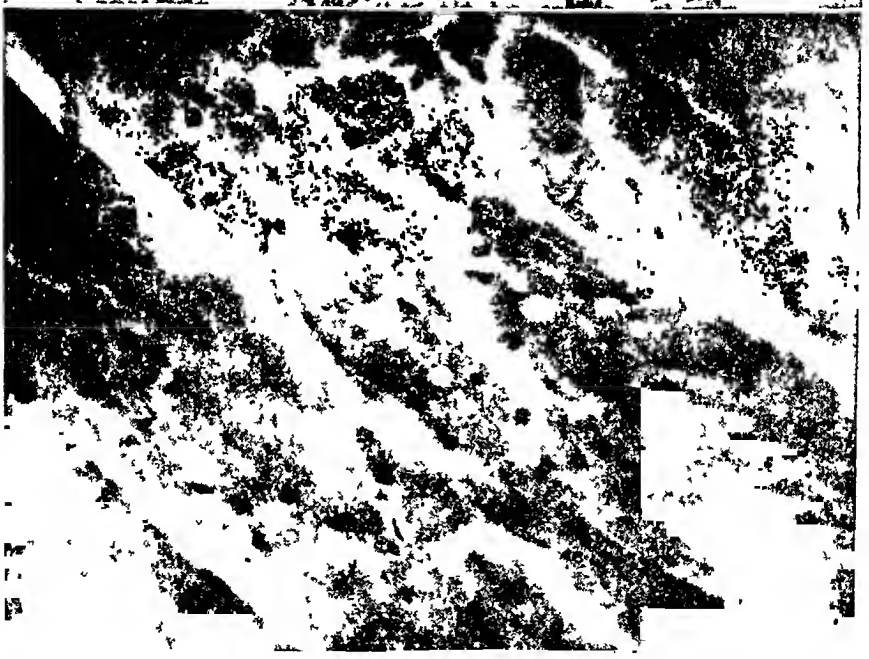


Fig 10 *(above)* Lung of a guinea pig killed with Sympathin, showing intense alveolitis with giant cells with the nucleus in the center of the cell (Langerhans type)

Fig 11 *(below)* Myocardium of a guinea pig killed with Sympathin, showing vacuolar degeneration of the muscular fiber of the heart and cells with vacuoles of different sizes

All the control animals to which Sympathin was not given died. As a lethal dose, 1 5 mg. per kg of histamine has been found to be effective The introduction of the Sympathin was done in the intraperitoneal way, as it was also done with the guinea pigs The histamine was injected into

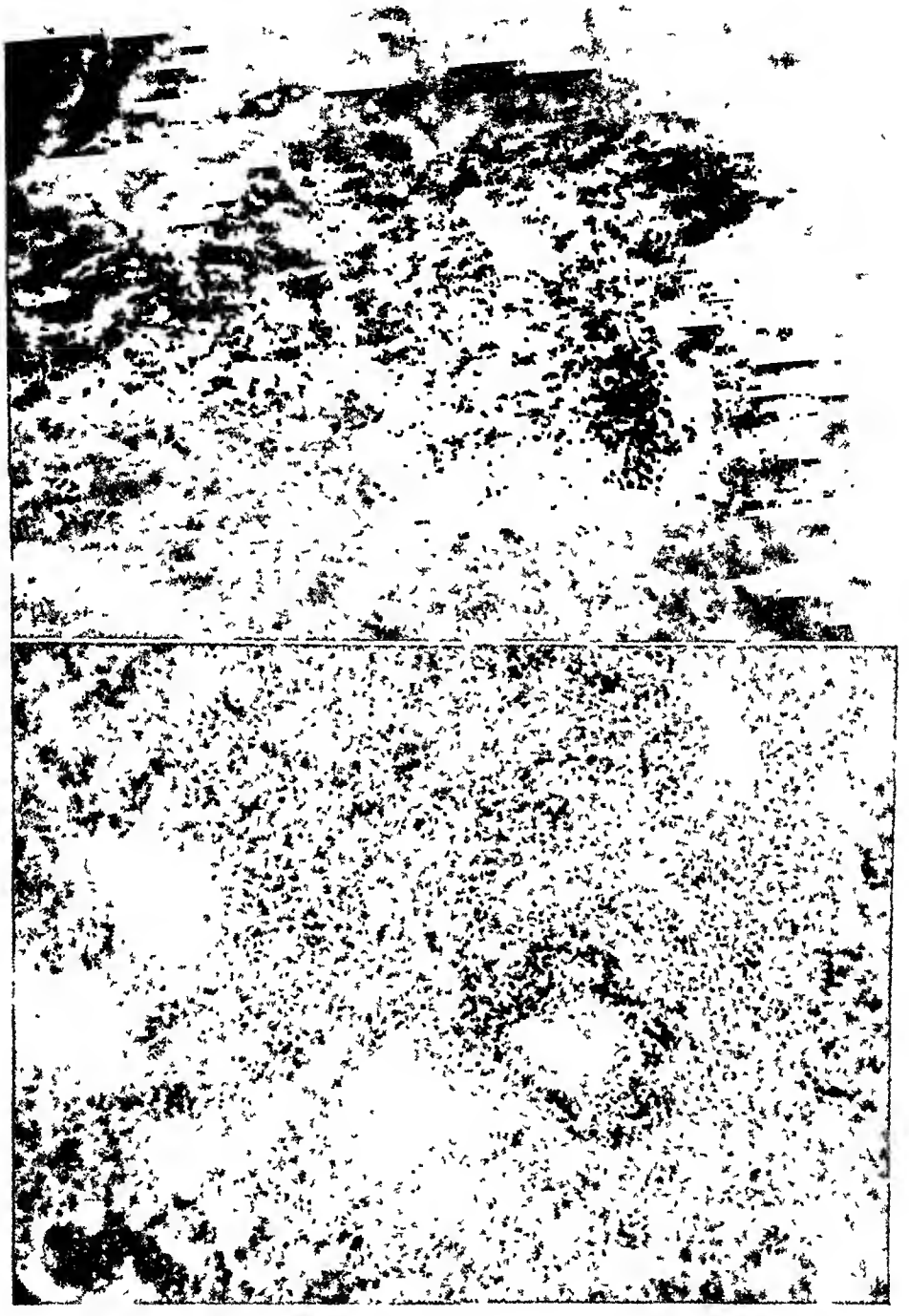


Fig. 14. *(above)* Myocardium of a rabbit killed with Sympathin, showing infiltration of round cells of the lymphocytic type.

Fig. 15. *(below)* Lung of a rabbit killed by Sympathin, showing a vessel with an infiltration of round cells of the lymphocytic type, with intense hemorrhagic alveolitis.

the marginal vein of the ear. The results can be seen in Table IV, where it will be observed that there were 83.3 per cent rabbits without shock, 8.3 per cent with moderate shock, and 8.3 per cent with shock.

TABLE IV. ANTIHISTAMINIC ACTIVITY OF SYMPATHIN IN THE PRESENCE OF LETHAL DOSES OF HISTAMINE IN RABBITS

	1	2	3	4	5
	No.	Weight	Sympathin Injected	Histamine Injected	Shock
Group A:	1	1,930	0.95 c.c.	2.9 mg.	Yes
	2	2,330	1.15 c.c.	3.5 mg.	Yes
	3	1,870	0.90 c.c.	2.8 mg.	Yes
Group B:	1	1,500	12.8 c.c.	2.25 mg.	No
	2	1,320	5.5 c.c.	1.98 mg.	No
	3	1,350	5. c.c.	2.0 mg.	No
Group C:	1	1,720	6.36 c.c.	2.58 mg.	No
	2	1,590	5.88 c.c.	2.38 mg.	No
	3	1,850	6.84 c.c.	2.77 mg.	No
	4	1,750	6.47 c.c.	2.52 mg.	No
	5	2,250	8.25 c.c.	3.34 mg.	Yes
	6	1,810	6.69 c.c.	2.71 mg.	No
	7	1,620	5.99 c.c.	2.43 mg.	No
	8	1,520	5.62 c.c.	2.28 mg.	No
	9	1,480	5.47 c.c.	2.22 mg.	No
	10	1,560	5.77 c.c.	2.24 mg.	Yes

Column 2: Weight of the animals.
Column 3: Sympathin injected intraperitoneally.
Column 4: Histamine chlorhydrate injected endovenously.
Lethal dose 1.5 mg. per kg. injected fifteen minutes after the Sympathin in Group A. In groups B and C injections were given when the first symptoms of sympathinic intoxication appeared.

TABLE V. REINJECTION OF LETHAL DOSES OF HISTAMINE IN 4 RABBITS WHICH HAD BEEN INJECTED WITH SYMPATHIN AND HISTAMINE 12 DAYS BEFORE

1	2	3	4
No. of Animal	Weight	Histamine in Mg.	Shock
3	1,770	7.98 (3 L.D.)	No
8	1,550	2.32 (1 L.D.)	No
7	1,700	4.9. (2 L.D.)	Yes
9	1,440	6.48 (3 L.D.)	No
C	1,080	1.6 (1 L.D.)	Yes

1st column: Number of animal of the third group in Table IV. C means control.
2nd column: Weight of animal.
3rd column: Histamine injected intravenously, one lethal dose equal to 1.5 mg. per kg.
4th column: Shock means whether animal has had shock or not.

A group of four rabbits, which had been treated with Sympathin, were investigated as to whether they would be again able to survive, twelve days after the experiment, a histaminic shock with a dose two to three times lethal. The results found are given in Table V.

It will be seen therefrom that two of the rabbits survived three lethal doses, another one lethal dose. The fourth did not survive two lethal doses. In the same way as in the former experiment, all control animals died from histaminic shock on one lethal dose.

*Sympathin in the Presence of Inhaled Histamine***

The technique of inhalation of histamine has been carried out according to details given by the investigators who have gone into this question (Kallos and Pagel, Mayer, et cetera). The guinea pigs are placed in a glass receptacle of a capacity of about 19 liters and made to inhale, in the

**The histamine was kindly provided by the Laboratories of the Latin Pharmacological Institute: Lefa and Inter-Carulla.

TABLE VI. ANTIHISTAMINIC ACTIVITY "IN VIVO" INHALATION OF HISTAMINE IN GUINEA PIGS

1	2	3	4	5				6
	Weight in	Before Sympath-	Sympath-	Time after Sympathin				Time of increased
No.	Gm.	in	in	15 min.	1 hr.	2 hr.	24 hrs.	protection
1st Group:								
1	385	1'10"	3 c.c.		4'			Yes
2	450	1'20"	3 c.c.		5'30"			Yes
3	450	9'		2'				No
4	430	1'30"	3 c.c.					
5	445	3'	2 c.c.					
6	350	1'30"	2 c.c.	1'40"				Yes
7	325	1'30"	2 c.c.		1'45"			Yes
8	405	1'	1 c.c.	1'25"				Yes
9	535	30"	1 c.c.	2'30"		3'40"		Yes
10	440	1'30"	1 c.c.	1'40"				Yes
C. 11	445	2'30"						—
2nd Group:								
1	395	1'30"	2.6		1'32"	1'40"	1'26"	Yes
2	500	45"						—
3	280	1'20"	1.8		3'15"	1'30"	-de 7'	Yes
4	345	1'10"	2.3		30"	56"	2'36"	Yes
5	485	40'	3.2					
6	440	1'27"	2.9		1'15"	1'6"		No
7	265	40"	1.7		1'22"	1'7"	0	Yes
8	305	1'15"	2		1'17"	1'20"	1'40"	Yes
9	300	55"	2		55"	45"	30"	No
C. 10	280	1'			40"	-de 3'		Yes
3rd Group:								
1	395	1'26"	4 c.c.	2'7"				Yes
8	305	1'40"	4 c.c.	1'41"				No
9	300	30"	4 c.c.	35"				Yes

1st column: In the third group the guinea pigs 1, 8 and 9 are the same as 1, 8 and 9 of the second group injected again with Sympathin after twenty-four hours.
C. means control.
2nd column: Weight of animals.
3rd column: Time in minutes and seconds in which occur the first convulsions. Time control of convulsions.
4th column: Quantity of Sympathin injected intraperitoneally.
5th column: Means time in which appears the first convulsions retested on the animal by inhalation of histamine after fifteen minutes, one hour, two hours and twenty-four hours.
6th column: Means if the injected Sympathin protects the animal or not.

form of aerosol, a solution of chlorhydrate of histamine at 1 per cent and at a speed of 15 liters per minute under pressure from an oxygen tank.

The figures of histaminic sensitivity found by us in these experiments are smaller than those given by other investigators, which we attribute to the capacity of the recipient. The first convulsions, sign of histaminic intoxication, appeared in the animal after about fifteen minutes, and not three or 3.5 minutes as mentioned by other authors. The results of the inhalation of histamine by twenty-four guinea pigs are shown in Table VI. From this, we can observe that once injected with Sympathin, as per the quantities given in this table, there were 78.9 per cent of the animals which survived the shock, including some which did so only after twenty-four hours (Guinea pigs 3, 4 and 7 of the second group).

DISCUSSION

The similarity of the pharmacological behavior of epinephrine with Sympathin led us to study, as we had previously done with epinephrine, the action of histamine on Sympathin presents in the organs of recently killed animals. From this group of experiments it may be seen that Sympathin, as epinephrine, plays an important part in the regulation of histaminic level,

provoking its liberation and acting as a regulating mechanism. Following up the existence of this similarity, and remembering that Loew and his collaborators placed epinephrine among the most powerful antihistaminics, we investigated the antihistaminic reaction of Sympathin.

This was shown effectively to possess an obvious and lasting antihistaminic action, contrary to what takes place with synthetic antihistaminics, which act only when present in the blood stream or in the cells. In favor of these drugs it may be stated that they possess a high antihistaminic power, for which reason they are of absolute necessity in the treatment of allergic diseases. However, Sympathin can compete with them as to its lasting effects, since it has shown activity even twelve days after having been injected. This leads us to suppose that its mechanism of action is different to that which antihistaminics in series are believed to possess. It is the general opinion that they neither neutralize the histamine in the blood, nor activate the histaminase, but rather displace the histamine from its point of action with regard to Sympathin. We believe, however, that through it mechanisms of compensating regulation are put into play.

SUMMARY

Extracts of different organs with marked adrenergic power have been obtained, as has been proven by their action on the blood pressure of dogs and cats.

After a study of the action of the histamine of the dog, parallel to that of its arterial pressure under the effects of Sympathin, it was seen that, while the average blood pressure values in eight tests increased from 14.9 to 17.5 cm. Hg., the histamine in the blood was also increased from 0.6 to 1.05 micrograms per hundred c.c. of blood.

Control dogs, injected exclusively with a depressor extract, showed a decrease of histamine, at the same time as there was a descent in arterial pressure.

After a study of the behavior of Sympathin in the intestinal loop of the guinea pig, an antihistaminic and antiacetaylcholinic effect was proved. The action of Sympathin was also studied, when lethal doses of histamine were present in guinea pigs and rabbits, previously treated with adequate doses of Sympathin. Of fifteen guinea pigs that were injected with a lethal dose of histamine, nine survived the histaminic shock, a proportion of 60 per cent; of twelve rabbits injected with a lethal dose of histamine, ten survived the shock, or 83.3 per cent.

A group of four rabbits, that had been treated with Sympathin twelve days previously, was investigated to determine whether they were still able to survive histaminic shock. It was found that two of them survived three lethal doses; one survived one lethal dose; and another died

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AN APPROACH TO THE PROBLEM OF "EPINEPHRINE FASTNESS"

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A DISTRESSING clinical problem is that of "epinephrine fastness." This is a poor term in a sense, yet descriptive of that condition presented by the patient whose bronchial asthma has not responded favorably to successive doses of epinephrine; the patient has become refractory to the drug's usual dramatic bronchodilating action in this form of allergy.

The administration of oxygen as well as intravenous glucose or aminophylline has frequently corrected this refractoriness to epinephrine but a new, plausible approach is suggested by correlation of several recent reports dealing with the effect of antihistaminic agents on certain functions controlled by the autonomic nervous system.

Staub[5] demonstrated that epinephrine invoked the production or release of histamine in the experimental animal, probably as a homeostatic effort; this has been adequately confirmed by Farrerons-Co.[1] These reports probably explain in part the mechanism involved in the potentiation of adrenergically controlled functions by antihistaminic agents,[6] since a normal response to epinephrine, such as hypertension, might well be enhanced due to the inhibition of antagonistically acting (hypotensive) histamine. Thus, in a sense, the "sparing of epinephrine" need not necessarily be only retardation of its chemical degradation by Pyribenzamine or Benadryl[6] and related compounds but merely a taking away of the histamine brake from the histamine-sympathin balance.

The work of Staub and Farrerons-Co undoubtedly also explains in part the marked pulmonary edema which can be experimentally produced by successive injections of epinephrine[2] through the medium of histamine. The important observation of Halpern and Cruchaud[3] that the antihistaminic agent 3277 R.P. prevented such edema, in our conception, further supports the observations of Staub and Farrerons-Co, and we believe that an important clinical application is hereby suggested, namely, the use of antihistaminic agents in the so-called "epinephrine fast" or epinephrine resistant patient. The following train of events might be considered:

1. Epinephrine calls forth histamine, probably more so in the allergic than in the normal subject.

2. Although epinephrine relaxes the bronchial musculature, this favorable feature could be counterbalanced by histamine's strong propensity to contract this muscle. The state of such muscle would obviously depend upon whether epinephrine or histamine predominated functionally.

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3. Although epinephrine might relax the bronchi, histamine's secretagogic effect probably is so marked that the bronchial lumina would be considerably reduced functionally and thus account for severe pulmonary edema with its associated air hunger; furthermore, if histamine's constricting action on the bronchial musculature predominated over that of epinephrine's relaxing effect, the situation would be still further aggravated.

4. An antihistaminic agent like those now available should inhibit clinically the edema promoting action of histamine as Halpern and Cruchaud[3] demonstrated experimentally. Such therapy should also nullify contraction of the bronchial musculature by histamine and thus allow epinephrine's bronchodilating effect to predominate and probably be potentiated, with attending dramatic relief of the gasping asthmatic to be anticipated. Successive doses of epinephrine, if further indicated therapeutically, should then only act favorably to relax the bronchi in the presence of specific antihistaminic therapy. In view of these probable events the injection of the antihistaminic agent in this emergency seems rational.

Dr. Maurice S. Segal of Boston has recently informed us[4] that he has successfully treated epinephrine fastness in two cases by the intravenous use of an antihistaminic agent. As a matter of fact, he now includes this clinical condition "along with paranasal sinus disease and sino-bronchitic disease as an indication for the use of an antihistaminic preparation in the management of very sick asthmatic subjects." He further states that "the appearance of the epinephrine-fast patient who continues to receive epinephrine certainly resembles the patient receiving large amounts of histamine during one of our protective studies."

"Epinephrine fastness," although descriptive of a clinical condition, is unsatisfactory from a pharmacologic point of view. Actually, if the whole pharmacology of epinephrine be borne in mind, this disconcerting clinical condition represents nothing more than a specialized form of toxic reactions to epinephrine, exercised through the medium of histamine. Hence, a formerly obscure and unsatisfactory term, "epinephrine fastness," apparently becomes clarified through successive experimental demonstrations of the complete pharmacology of not only epinephrine but also of histamine and antihistaminic agents in this regard.

REFERENCES

1. Farrerons-Co, F. J.: Histamine-Sympathin balance. Ann. Allergy, 6:46, (Jan.-Feb.) 1949.
2. Hallion and Nepper: J. Physiol. Pathol. gén., 13:887, 1911.
3. Halpern, B. N., and Cruchaud, S.: Prevention de l'oedème aigu expérimental du poumon par un antihistaminique de synthèse dérive de la thiodiphénylamine Experientia, 4:34, 1948.
4. Segal, M. S.: Personal communication.
5. Staub, H.: Die Adrenalin-Histamin-Regulation, mit Beitrag zum Antistammechanismus. Schweiz. med., Wchnschr., 76:818, 1946.
6. Yonkman, F. F.: Adrenergic potentiation, a pharmacodynamic effect associated with antihistaminic agents. Am. J. Digest. Dis., 14:360, (Nov.) 1947.

HOUSE IVY DERMATITIS

Treatment by Alcoholic Extract of House Ivy Leaves

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IN 1927, Spain and Cooke[10] demonstrated that absolute alcohol extracts of oleoresinous substances in poison ivy leaves could be used for the diagnosis and treatment of Rhus dermatitis. Four years later, in 1931, Brown, Milford, and Coca[2] showed that ragweed dermatitis was due to the fat-soluble fraction of the plant or pollen, and suggested that treatment should be attempted with the oleoresin dissolved in almond oil. Subsequently, attention was focused on the use of oily solutions of oleoresins in the treatment of plant dermatitis. The successful treatment of ragweed and other plant dermatitis with oleaginous extracts was reported by a number of investigators, including Brunsting and Williams,[3] Pascher and Sulzberger,[7] Frank,[6] Caulfield,[4] Rudolph and Deutsch,[8] and Seyler.[9]

However, the therapeutic administration of oil extracts presents certain disadvantages. The deep intramuscular injections required are frequently painful for several days. The injected oil is absorbed at a slow rate, and thus there may not be sufficient contact with the body cells to produce a high degree of immunologic response. The presence of minute quantities of protein in the oily medium, especially when peanut oil is used, may cause severe reactions in a person allergic to the menstruum.

In an attempt to overcome these disadvantages, Clarke and Ricchiuti[5] reverted to the method of Spain and Cooke and prepared an extract of ragweed leaves in absolute alcohol. With this alcoholic extract they were able to treat ragweed dermatitis successfully. It, therefore, became apparent that alcoholic extracts of dermatitis-producing plant oleoresins were therapeutically effective in conditions other than Rhus dermatitis. The significance of this observation lies in the fact that alcoholic extracts present several advantages over oil extracts. They are more easily prepared and diluted. By means of patch tests with serial dilutions, the exact degree of individual sensitivity may be evaluated and dosage can be adjusted accordingly. The alcoholic extracts are given by deep subcutaneous injection, and this is only momentarily painful. Because of its distribution in the subcutaneous tissues, the antigenic material is more rapidly absorbed, providing a more effective immunologic response, of special importance in phylactic treatment. There is no danger of allergic sensitivity to the solvent.

The ease with which alcoholic extracts of plant leaves can be prepared should warrant the therapeutic trial of such extracts in cases of dermatitis venenata from plant sensitivity. A large variety of plants is capable of giving rise to such conditions: Weber[11] in 1937 listed 113 "irritating plants of the U. S." In a few rare instances, house ivy has been cited as an

Fig. 1. Positive patch test to alcoholic extract of ivy leaves.

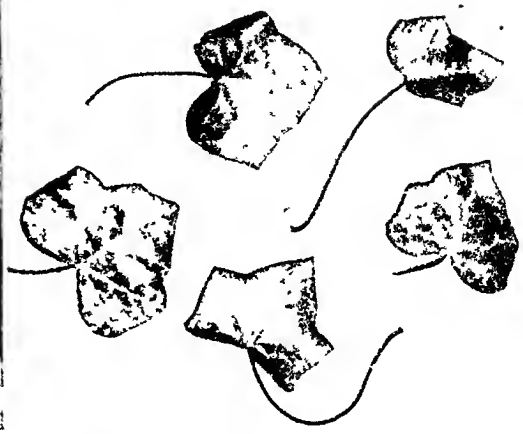

Fig. 2. Specimen leaves of English ivy causing the dermatitis

offending factor. (Seyler,[9] Weber,[11] Aleman and Vall.[1]) The following case report illustrates the management of house ivy dermatitis with a simple alcoholic extract of the ivy leaves.

CASE REPORT

G. M., a man of fifty-one, was first seen on May 4, 1946, with a history of a summer rash of seven or eight years' duration. The usual sites of involvement were the hands, feet, and the region behind the ears. The attacks occurred in bouts, lasting three or four days, with several exacerbations during the summer months. On one occasion, after having cut down some house ivy and trampled it into a basket, he developed an extensive dermatitis of the hands and feet which necessitated confinement to bed for several days. The diagnosis of dermatitis venenata due to house ivy was suspected, and a confirmatory patch test was made with a house ivy leaf secured from the patient's own home. This gave a definitely positive reaction The patient's home was covered with English ivy (hedera helix), to which he was found sensitive. However, a patch test with a leaf of Boston ivy (parthenocissus tricuspidata) was negative

A quantity of the English house ivy leaves was then collected and an alcoholic extract prepared in the following manner. The leaves were desiccated by air on a laboratory table and later on top of a dry air sterilizer. The dry leaves were broken up, and 10 grams were immersed in 100 c.c. of absolute alcohol for a period of twenty-four hours and then filtered through dry paper. A preliminary patch test with a 1 :100 dilution of this extract failed to produce a reaction, but a subsequent test with the undiluted extract was strongly positive. Control tests made on ten other persons were negative

Prophylactic treatment was begun on May 11, 1946, with 0 25 c c. of a 1 1,000 dilution of the alcoholic extract of the house ivy leaves. The injections were administered by the following technique. The amount of extract required was withdrawn into a dry tuberculin syringe. To this was added sufficient buffered saline solution to make a total volume of 0 3 to 0.4 c c, and the syringe was rapidly inverted two or three times The active principle of the alcoholic extract was at once thrown out of solution into a finely divided suspension with an opalescent appearance.

This suspension was immediately injected deeply into the subcutaneous tissue of the arm, using a 26-gauge, ½-inch hypodermic needle.

The prophylactic injections were continued at intervals of four to seven days until a level of 0.2 c.c. of a 1:10 dilution was reached in five weeks. The maximum dose was repeated in July and again in August. The result of the treatment was completely satisfactory, since, for the first time in many years, the patient remained free of his usual summer rash.

On the basis of the successful application of treatment with alcoholic extracts to such divergent conditions as Rhus, ragweed, and house ivy dermatitis, it is felt that a similar approach can be employed in cases of dermatitis venenata in which a plant sensitivity is suspected. A preliminary patch test should be made with a leaf of the suspected plant, and if this proves positive, a simple alcoholic extract can be easily prepared within twenty-four to forty-eight hours. The sensitivity of the patient can then be calibrated by patch testing with the alcoholic extract, and either phylactic or prophylactic treatment promptly instituted.

REFERENCES

1. Aleman and Vall: Rev. Clin. Espan., 9:426, 1943.
2. Brown, A.; Milford, E. L., and Coca, A. F.: J. Allergy, 2:301, 1931.
3. Brunsting, L. A., and Williams, D. H.: J.A.M.A., 106:1533, 1936.
4. Caulfield, A. H. W.: Canad. M. A. J., 34:506, 1936
5. Clarke, J. A., and Ricchiuti, J. F.: Arch. Dermat. & Syph., 41:551, 1940.
6. Frank, J. J.: J. Iowa M. Soc., 25:283, 1935.
7. Pascher, F., and Sulzberger, M. B.: Arch. Dermat. & Syph., 28:223, 1933.
8. Rudolph, J. A., and Deutsch, J.: J. Allergy, 9:187, 1938.
9. Seyler, L. E.: Ohio State M. J., 35:607, 1939.
10. Spain, W. C., and Cooke, R. A.: J. Immunol., 13:93, 1927.
11. Weber, L. F.: Arch. Dermat. & Syph., 35:129, 1937.

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HISTAMINE-SYMPATHIN BALANCE

(Continued from Page 59)

after two lethal doses. All control animals died from histaminic shocks, as did those which had received insufficient quantities of Sympathin.

In an investigation of the use of inhalation in preventing histaminic shock in guinea pigs, it was found that 78.9 per cent survived the shock after this procedure.

Sympathin, being a physiological substance extracted from normal organs, and a constant component of them, is among those factors which must be taken into account in the regulation of histamine.

I wish to express my heartiest thanks to Prof. Jimenez-Vargas for his interest and encouragement given me during my investigation. I also thank my colleagues of the Section of Human Physiology of the Spanish Institute of Physiology and Biochemistry and particularly Miss M. R. Bodi and Miss M. C. Lasso de la Vega for their collaboration.

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THE USE OF CEVITAMIC ACID IN THE SYMPTOMATIC AND COSEASONAL TREATMENT OF POLLINOSIS

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THE value of large doses of cevitamic acid in the control of allergic coryza was first observed, in 1938, as used in association with calcium ascorbate.[16] Until then, the currently accepted daily dosage of Vitamin C was 40 to 60 mg. With the introduction of calcium ascorbate, it was possible to inject as much as 450 mg. Since it was administered intramuscularly, a dose could be considered equivalent to double the quantity taken orally. Immediately subsequent to these studies, Jolliffe[11] stated that the therapeutic levels might be more than 1,000 mg. daily.

It was soon apparent that cevitamic acid might act at two "levels," functioning as a vitamin when given in small amounts, and as a drug when given in massive doses.[8] One such effect, the diuretic action, has been evaluated.[9]

Since Vitamin C may act by means of a number of mechanisms, determinations were made to discover whether the apparent beneficial effects seen in both infectious and allergic coryza were due to the Vitamin C, the calcium, or both.[16] For this purpose, the anti-histamine effect of Vitamine C and calcium ascorbate were studied by the microscopic examination of bronchiolar reactions.[16] The results of these investigations, presented at the American Chemical Society in 1940, demonstrated that Vitamin C and calcium ascorbate possessed anti-histamine properties, while calcium gluconate had a histamine-like action and would thus present no anti-allergic activity.

In 1942, Holmes[10] reported a similar use of Vitamin C in daily doses ranging from 250 to 1,000 milligrams. Taken orally by the five patients studied, it was said to have caused an objective clinical improvement. Following this report, various clinical impressions contradictory as to the usefulness of Vitamin C in allergy, were published. These have been reviewed by Brown.[3]

While it was possible to secure animal experimental study on the anti-histamine effects of Vitamin C, it was extremely difficult to devise satisfactory objective experiments with patients, especially since Cody[5] had stated that vasomotor rhinitis might be an early symptom of latent or subclinical scurvy. It was, therefore, decided to study a moderately large clinical group of subjects presenting a similar condition, namely, hay fever, under completely independent observations in two cities of equivalent pollen seasons, Boston and New York. Unmarked tablets of Vitamin

REPORT ON STUDIES IN BOSTON

43 Patients

1. How many seasons of hay fever?
   1 to 36 years.
2. Food allergy also present:
   None—19
   Some—3
   Doubtful—21.
3. Concomitant attacks of bronchial asthma:
   No—26
   Yes—15.
4. First hay fever symptoms by date:
   Earliest—May 15
   Latest—September 13.
5. How would you consider your present attacks as measured against previous years?
   Worse—10
   Same—11
   Better—19
   Doubtful—3 (first season of hay fever).
6. The effects of increasing the dose gave results as:
   Same—12
   Better—8
   Others—3
   No increase—20.
7. Do you think the tablets were:
   Not helpful—16
   Helpful—25
   Doubtful—3.
8. Did the tablets cause gastric irritation?
   No—34
   Yes—4
   Doubtful—5
   The doubtful patients did not take a sufficient amount to enable them to judge.
9. Any increase in urination?
   No—38
   Yes—0
   Doubtful—5 (sufficient amount not taken).
10. Do you feel generally
    Same—8
    Worse—8
    Better—22
    Doubtful—5 (sufficient amount not taken).
11. Did you also receive injection treatment for hay fever?
    No—13
    Yes—30.
12. Have you received injections in previous years?
    No—33
    Yes—10.
13. Do you consider the tablets modified your attacks?
    No—21
    Yes—21
    Doubtful—5 (sufficient medication not taken).

C with elements of Vitamin B Complex were made available to us. Each tablet contained ascorbic acid, 250 mg. and thiamine, 1 mg.

The doses varied from one tablet four times daily to three tablets three times daily; that is, 1,000 to 2,250 mg. daily.

The following questionnaires were collected from each patient at the end of the pollen season. Although the reports were purely clinical, it is interesting to note that approximately similar results were obtained by both observers. The data are tallied in the accompanying reports.

REPORT ON STUDIES IN NEW YORK

27 Patients

1. How many seasons of hay fever?
   1 to 35 years.
2. Food allergy also present:
   No—15
   Yes—12.
3. Concomitant bronchial asthma:
   No—12
   Yes—15.
4. Date of first hay fever symptoms:
   Mid-May—5
   June—1
   August—17
   September—4.
5. How would you consider your attacks as compared to previous years?
   Worse—3
   Same—6
   Less—14
   Doubtful—4 (First season of hay fever).
6. Did increase in dosage give:
   Same—0
   Better—18
   Other—9 (Either no effect or doubtful).
7. Do you think the tablets were:
   Not helpful—5
   Helpful—20
   Doubtful—2.
8. Did the tablets cause gastric irritation?
   No—17
   Yes—6
   No answer—4.
9. Any increase in urination?
   No—17
   Yes—10.
10. Do you feel generally:
    Same—4
    Worse—4
    Better—17
    Doubtful—2 (First year of symptoms).
11. Did you receive injections for hay fever?
    No—15
    Yes—9
    No answer—3.
12. Have you received injections for hay fever in previous years?
    No—15
    Yes—9
    No answer—3.
13. Do you consider the tablets modified your attacks?
    No—3
    Yes—24.

Although it has been shown by a number of observers that a Vitamin C deficiency will affect the susceptibility of animals to allergization, there are reports which indicate a lack of such effects. Among negative reports are those of Cohen[6] and of McDonald and Johnson,[13] who stated that Vitamin C had no effect upon an animal's capacity for becoming sensitized eczematogenously to arsphenamine or to poison ivy or on the animal's tendency to go into anaphylactic shock. Dragstedt and his colleagues[7] reported that the administration of Vitamin C, prior to the induction of peptone shock, failed to prevent anaphylactic reactions in dogs, stating that Vitamin C did not inhibit the liberation of histamine.

Walther,[19] using both guinea pigs and rabbits, pretreated for seven days with large amounts of Vitamin C, and then, shocked by the intratracheal introduction of the specific pneumococcus antigen, made histologic studies of the tissues. He stated that the Vitamin C did not decrease the local anaphylactic pulmonary response and, in some cases, seemed to intensify it. Ardy[1] reported that guinea pigs showed no variation in the amount of their blood complement when kept on either high or low Vitamin C diets. In 1938, Walzer[20] stated that it had not been proved that Vitamin C had played a definite role in human hypersensitivity. Bundesen,[4] in 1941, maintained that there was no clear evidence that Vitamin C intake could affect allergic conditions. Sulzberger and Oser[18] reported, in 1935, that guinea pigs could be sensitized to arsphenamine much more readily when deficient in Vitamin C than when taking normal or decreased amounts. Steinbach and Klein[17] affirmed that in animals there was an increased tolerance to tuberculin when sufficient cevitamic acid was given. Kile and Pepple[12] observed that those animals showing marked Vitamin C deficiency, could be sensitized. Yoshikawa[21] helped solve the problem with his report that guinea pigs were more easily sensitized when given small quantities of Vitamin C, but were incapable of being sensitized when given large amounts. When there was a moderate intake, there was no effect.

As previously mentioned, the subject has been reviewed recently by Brown.[3] Other reviews, which may be consulted by the interested reader, include those by Banerjee[2] and by Pijoan,[14] each giving a picture of the complexity of the subject. The inter-relationship between Vitamin C, protein metabolism, calcium, and other minerals,[15] such as manganese, have not yet been explored fully. The work of Yoshikawa[21] is therefore of special interest. His statement that the administration of daily doses of 2.5 mg. of Vitamin C increased the allergic sensitivity in guinea pigs, while moderate doses had no effect and larger doses (100 mg.) possessed an inhibiting influence, evidently is of great importance. Especially to be noted as an essential part of the present investigation is the magnitude of the dose employed.

An extremely skeptical analysis of the forty-three questionnaires by one of us (EAB), gave the following impressions:

Three patients, F. D., M. C., and N. N., complained of ill effects, due supposedly to the medication. The first patient stated that the tablets were laxative and the second and third reported flushing of the head and shoulders and severe headaches. If these symptoms were due to the Vitamin C and the B Complex, it would suggest that approximately 5 per cent of the patients might suffer mild, although easily controlled, side reactions.

Two patients, C. S., and H. M., were difficult to evaluate. The first patient followed a pattern similar to that of the previous year and felt that her symptoms were decreasing at the time of the Vitamin C ingestion. She stated that she was certain she would have improved without medication. The second patient, who had tree and grass pollen sensitivity, was given doses of 600 mg. daily after his tree symptoms had been present for two weeks and the pollen count had decreased. He left Boston at the beginning of the grass season and did not communicate with the

physician for a further supply of medicine. His hay fever was especially severe during June and July. Neither of these patients can be used for statistical purposes.

Ten patients reported that their attacks were the same as in previous years, and that they could see no difference in their symptoms after taking four tablets daily for one week. Analysis of their histories showed that their symptoms were of the same severity before they started taking the tablets, during the time they took them, and for the remainder of the season after they ceased taking them. Forty tablets, four daily for ten days, had no demonstrable effect upon their condition.

Of these patients, three, C. P., H. P., and J. W., suffered from pollen asthma. One of this group, J. W., and another, N. P., were clinically sensitive to foods. These foods supposedly were eliminated from their diets during the period of treatment.

Eight patients complained that they were much worse while taking the tablets. Two of the patients in this group began to improve as soon as they were given co-seasonal intradermal doses of ragweed pollen extract. Three of the patients, S. B., J. G., and E. C., felt that a one-week period was not a sufficient trial, but it was concluded that since they actually felt worse for the week of medication, there was no point in giving them higher doses, or additional treatment.

The patients, who reported that they could see no measurable effects or were worse, totalled eighteen. Those who said they were improved totalled nineteen, an almost equal number. The majority of the patients were requested to report that they were not improved unless it was very clearly and objectively noticeable, and unless the improvement could be termed at least a 50 per cent or a much greater change as compared to the previous season.

One patient, in this group, P. B., presented a vasomotor coryza, perennial in type. While still taking the Vitamin C tablets she suffered a recurrence of her condition and therefore is only classified for the time period between August 15 and October 1. Fourteen of the patients in this group had received injections of pollen extracts for their hay fever. In some instances, this was considered a sufficient amount of material to insure a fairly satisfactory result. In no instance, however, were the tablets given until the patient showed some symptoms, and in all of them the improvement seemed to occur within a day or two, and seemed to be directly related to the medication.

One patient, C. D., received intradermal doses of ragweed pollen extract (5 units) at weekly intervals. The remaining three of the nineteen who improved, had no co-seasonal treatment whatsoever, except occasionally a symptomatic type for nasal or ocular relief.

With as moderate and objective a conclusion as any clinical study warrants, it can be said that about half of the patients studied in Boston presented an improvement, which they judged to be greater than 50 per cent. These results would suggest that cevitamic acid therapy is suitable for the adjuvant treatment of pollinosis. A careful examination of the patients' histories showed no apparent reason for relief in some patients and none in others. The number who improved was not great. However, the reason for the present report, lies in the fact that in the patients whose conditions did improve, the change was quite striking, and occurred at any point in the season, within forty-eight hours after the initiation of Vitamin C therapy. It could be related neither objectively to any change in meteorologic conditions nor subjectively to purely psychologic factors.

An analysis of the patients studied in New York revealed the following:

Three took the Vitamin C tablets for a short period of time and found it of doubtful value. One of these patients, M. D., ceased treatment because of the appearance of periorbital urticaria. The other two subjects did not deem the treatment worthy of continuation.

Four patients felt that there was no benefit following the ingestion of the tablets, but nineteen patients reported benefit. Thirteen felt a marked improvement following the advancement of the dosage from 3 to 6 or 9 tablets daily.

The difference between the results in patients in Boston and those in New York may be attributed to the higher doses taken by the latter patients.

Only occasionally was there evidence of gastric irritation and there was an increase in diuresis. The feeling of well-being, experienced by the patients taking the tablets, was striking and was commented upon by both groups independently of the effect upon the pollinosis. Psychological factors, difficult to evaluate, may have played some part in these reports, especially since some patients wished to continue with the tablets after the pollen season had ended.

SUMMARY

A clinical survey of sixty patients, given Vitamin C during the ragweed hay-fever season, showed an improvement of 50 per cent or more in about half of the patients who took 250 mg. three or four times daily.

There were no untoward reactions, other than one instance of hives, and one patient, who, despite gastric irritation, continued the treatment. It may be concluded, therefore, that the use of cevitamic acid may be a suitable type of symptomatic adjuvant treatment for seasonal hay fever. It can be administered safely in doses ranging from 1,000 to 2,250 mg. daily.

While the analysis of the patients studied by one of us (EAB) showed a marked improvement in about half the number of the subjects, those studied by the other (SLR) demonstrated about three-quarters of the patients reporting improvement. This may be attributed to the fact that the former were kept on 3 or 4 tablets daily, while the latter were advanced to 6 or 9 tablets daily. The larger dose may have played a part in producing the apparently greater improvement in the larger percentage of patients.

REFERENCES

1. Ardy, C.: Complementary activity of the serum and Vitamin C. Rev. di. Clin. Pediat., 37:495, 1939.
2. Banerjee, S.: Vitamin C in health and disease. Science and Culture, 9:38, 1943. (119 references).
3. Brown, Ethan Allan: The vitamins and allergy. Ann. Allergy, 2:156, 1944 (56 references).
4. Bundesen, H. N.: Detoxifying action of ascorbic acid in arsenical therapy. J.A.M.A., 117:1692, 1941.
5. Cody, C. C.: Vitamin therapy in otolaryngology. Arch. Otolaryngol., 41:208, 1945.
6. Cohen, M. B.: Vitamin C deficiency. J. Allergy, 10:15, 1938.
7. Dragstedt, C. A., Eyer, S. W., and Arelland, M. R.: Vitamin C and peptone shock in dogs. Proc. Soc. Exp. Biol. & Med., 38:847, 1938.
8. Editorial: Vitamin C and infection. Lancet, 2:118, 1944.
9. Editorial: Ascorbic acid as a diuretic. Lancet, 2:186, 1944.
10. Holmes, H. N.: Hay fever and Vitamin C. South Med. & Surg., 105:56, 1943.
11. Jolliffe, N.: Preventive and therapeutic use of vitamins. J.A.M.A., 129:613, 1945.
12. Kile, R. L. and Pepple, A. W.: Further investigations of poison ivy hypersensitiveness in guinea pigs. J. Invest. Dermat., 1:59, 1938.

(Continued on Page 151)

PRELIMINARY PROGRAM

Fifth Annual Meeting

The American College of Allergists, Inc.

April 14-17, 1949

Palmer House

Chicago

NOTE The papers will not necessarily be presented in the order indicated in this preliminary program The titles of the papers and authors are also subject to change

George E. Rockwell, M.D.
Milford, Ohio
President, 1948-1949

Preliminary Program

FRIDAY, APRIL 15, 1949

Morning Session

Red Lacquer Room—9:00 A.M.

Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

The Mechanism of Infection and Immunity (animated movie)—HERMAN HEISE, M.D., Milwaukee, Wisconsin—*(15 minutes)*

Bronchoscopy (Color movie)—PAUL HOLINGER, M.D.,* Chicago, Illinois—*(30 minutes)*

Antigen—Antibody Mechanism in Neurotropic Virus Disease—BERRY CAMPBELL, Ph.D.,* and ROBERT A. GOOD, Ph.D., M.D.,* University of Minnesota—*(15 minutes)*

Intermission

Light Sensitivity Problems. Laboratory and Clinical Studies—CHARLES SHEARD, Ph.D.,* and BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota—*(30 minutes)*

Urticaria Photogenica. Report of Two Cases, One Associated with Purpura Photogenica—STEPHAN EPSTEIN, M.D., Marshfield, Wisconsin—*(15 minutes)*

Lunch

Afternoon Session

Red Lacquer Room—2:00 P.M.

Chairman: M. MURRAY PESHKIN, M.D., New York, New York

The Significance of Mediastinal Shift in Asthma—LESLIE OSMOND, M.D.,* and JAMES A. MANSMANN, M.D., Pittsburgh, Pennsylvania—*(20 minutes)*

Fungus Diseases of the Lungs and Bronchi—ABEL FROMAN, M.D.,* Chicago, Illinois—*(15 minutes)*

Late Non-Tuberculous Complications of Calcified Hylus Lymph Glands (so-called calcareous asthma)—JEROME HEAD, M.D.,* Chicago, Illinois—*(15 minutes)*

Intermission

Studies of Chronic Bronchitis—EMMET F. PEARSON, M.D.,* Springfield, Illinois—*(15 minutes)*

Chronic Cor Pulmonale in Bronchial Asthma—MAXWELL L. GELFAND, M.D., New York, New York—*(15 minutes)*

Asthma and the Heart—CLARENCE BIRNSTEIN, M.D., and S. D. KLOTZ, M.D.,* Orlando, Florida—*(15 minutes)*

*By invitation.

PRELIMINARY PROGRAM

FRIDAY, APRIL 15, 1949

Morning Session

Room 14—9:00 A.M.

Chairman: George E. Rockwell, M.D., Milford, Ohio

The Clinical Application of a New Piperazine Compound—Stanislaus H. Jaros, M.D., Tuckahoe, New York—*(10 minutes)*

Clinical Studies of Pyrrolazote—Henry Ogden, M.D.,* New Orleans, Louisiana—*(10 minutes)*

Results in Pollenosis with Combined Antigen—Antihistaminic Therapy—A. L. Maietta, M.D., Boston, Massachusetts—*(10 minutes)*

Enteric Coated Antihistaminics—S. William Simon, M.D., Dayton, Ohio—*(10 minutes)*

Intermission

A Combination of an Antihistaminic and a Sympathomimetic Drug in the Treatment of Hay Fever—M. H. Mothersill, M.D., Indianapolis, Indiana—*(10 minutes)*

The Relationship of the Antihistaminic Drugs as Shown by a Consideration of Their Structural Formulae—L. E. Seyler, M.D., Dayton, Ohio—*(10 minutes)*

Patient's Evaluation of Antihistaminic Drugs—Norman J. Ehrlich, M.D., and Morris Kaplan, M.D., Chicago, Illinois—*(10 minutes)*

Desensitization with Histamine-azo-protein: Review of the Literature and Report of 200 Personal Cases—Harry Weil, M.D., Milwaukee, Wisconsin—*(10 minutes)*

Lunch

Afternoon Session

Room 14—2:00 P.M.

Chairman: Orval R. Withers, M.D., Kansas City, Missouri

Further Studies on the Use of Tissue Culture of Blood Leukocytes in the Clinical Evaluation of Bacterial Hypersensitivity of the Tuberculin Type—Hermann Blatt, M.D., and Frank Nantz, M.D., Cincinnati, Ohio—*(10 minutes)*

Are Certain Dermatoses Bacterial Allergies—K. A. Baird, M.D., West St. John, New Brunswick, Canada—*(10 minutes)*

Multiple Sclerosis and Allergy Management—Hinton D. Jonez, M.D., Tacoma, Washington—*(10 minutes)*

Cerebral Allergy No. II—Epilepsy—Hal M. Davison, M.D., Atlanta, Georgia—*(10 minutes)*

Intermission

The Application of Aerosol Experiments in Animals—Vernon Bryson, M.D.,* and H. A. Abramson, M.D., New York, New York—*(10 minutes)*

Powdered Aerosols in Animals—Fred W. Wittich, M.D., Minneapolis, Minnesota—*(10 minutes)*

The Use of Bacitracin—a New Antibiotic—in Aerosol Form—Samuel J. Prigal, M.D.,* New York, New York—*(10 minutes)*

Aerosol Therapy: Presentation of Three Simple Methods—Stephan Lockey, M.D., Lancaster, Pennsylvania—*(10 minutes)*

*By invitation.

SATURDAY, APRIL 16, 1949

Morning Session

Red Lacquer Room—9:00 A.M.

Chairman: EDWARD G. TATGE, M.D., Evanston, Illinois

Mold Fungi in the Etiology of Respiratory Allergic Disease

IX. Intrinsic Fungous Factors in Relation to Asthma—L. O. DUTTON, M.D., El Paso, Texas—*(10 minutes)*

X. Aerobiological Fungus Populations—MARIE BLIZNER MORROW, Ph.D., Austin, Texas—*(10 minutes)*

XI. Further Studies with Mold Extracts—HOMER E. PRINCE, M.D., and Collaborators, Houston, Texas—*(10 minutes)*

XII. The Use of a Concentrated Extract in the Treatment of Mold-Sensitive Patients—KARL D. FIGLEY, M.D.,* Toledo, Ohio—*(10 minutes)*

Intermission

Molds and Inhalant Allergens—CLIFFORD KALB, M.D., Milwaukee, Wisconsin—*(10 minutes)*

The Role of Fungi in Patients with Bronchial Asthma and Anthracosis—J. W. PIFKARSKI, M.D., Wilkes-Barre, Pennsylvania—*(10 Minutes)*

Psychic and Somatic Factors in Eosinophilia—WILLIAM F. MITCHELL, M.D., Columbus, Ohio—*(10 minutes)*

Simplified Treatment of the Allergic Patient—J. MERCER ANDERSON, M.D., Salt Lake City, Utah—*(10 minutes)*

Lunch

Afternoon Session

Red Lacquer Room—2:00 P.M.

Chairman: HAL M. DAVISON, M.D., Atlanta, Georgia

Water and Electrolyte Disturbances in Status Asthmaticus: Etiology, Diagnosis, Treatment, and Prevention—MILTON M. HARTMAN, M.D., San Francisco, California—*(20 minutes)*

Continuous Aminophyllin Therapy in Status Asthmaticus II Further Observations—LEON UNGER, M.D., Chicago, Illinois—*(10 minutes)*

Observation on the Action of Orthoxine in Patients with Bronchial Asthma—SIDNEY FRIEDLAENDER, M.D.,* and ALEX S. FRIEDLAENDER, M.D., Detroit, Michigan—*(10 minutes)*

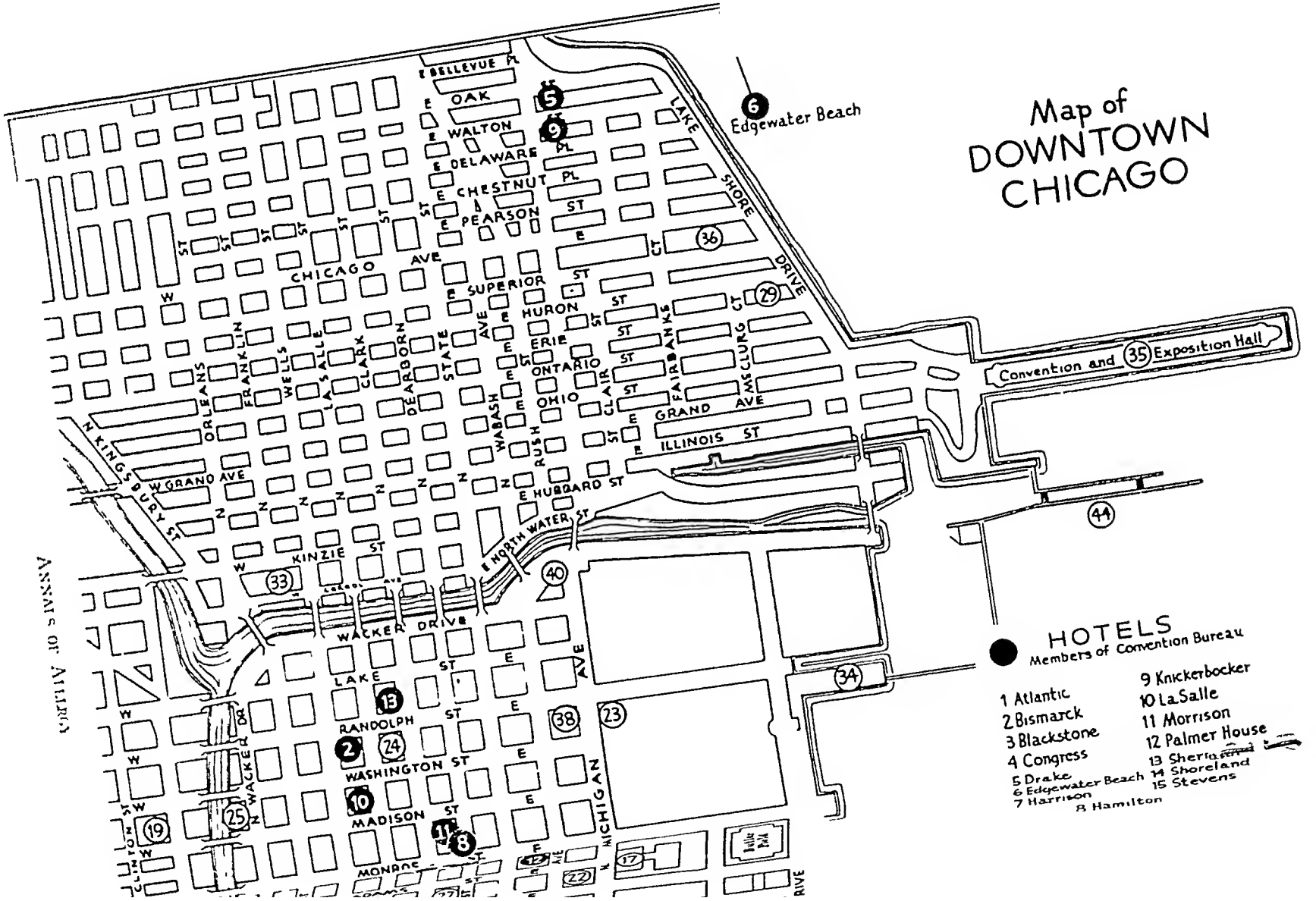
Intermission

Sudden Death from Asthma Presumably of Psychosomatic Origin—GEORGE WALDBOTT, M.D., Detroit, Michigan—*(10 minutes)*

Severe Asthma with Tracheotomy—SAMUEL R. ZOSS, M.D., Youngstown, Ohio—*(10 minutes)*

Bronchial Asthma in a Small Community Hospital—WILLIAM H. LIPMAN, M.D., Kenosha, Wisconsin—*(10 minutes)*

*By invitation.



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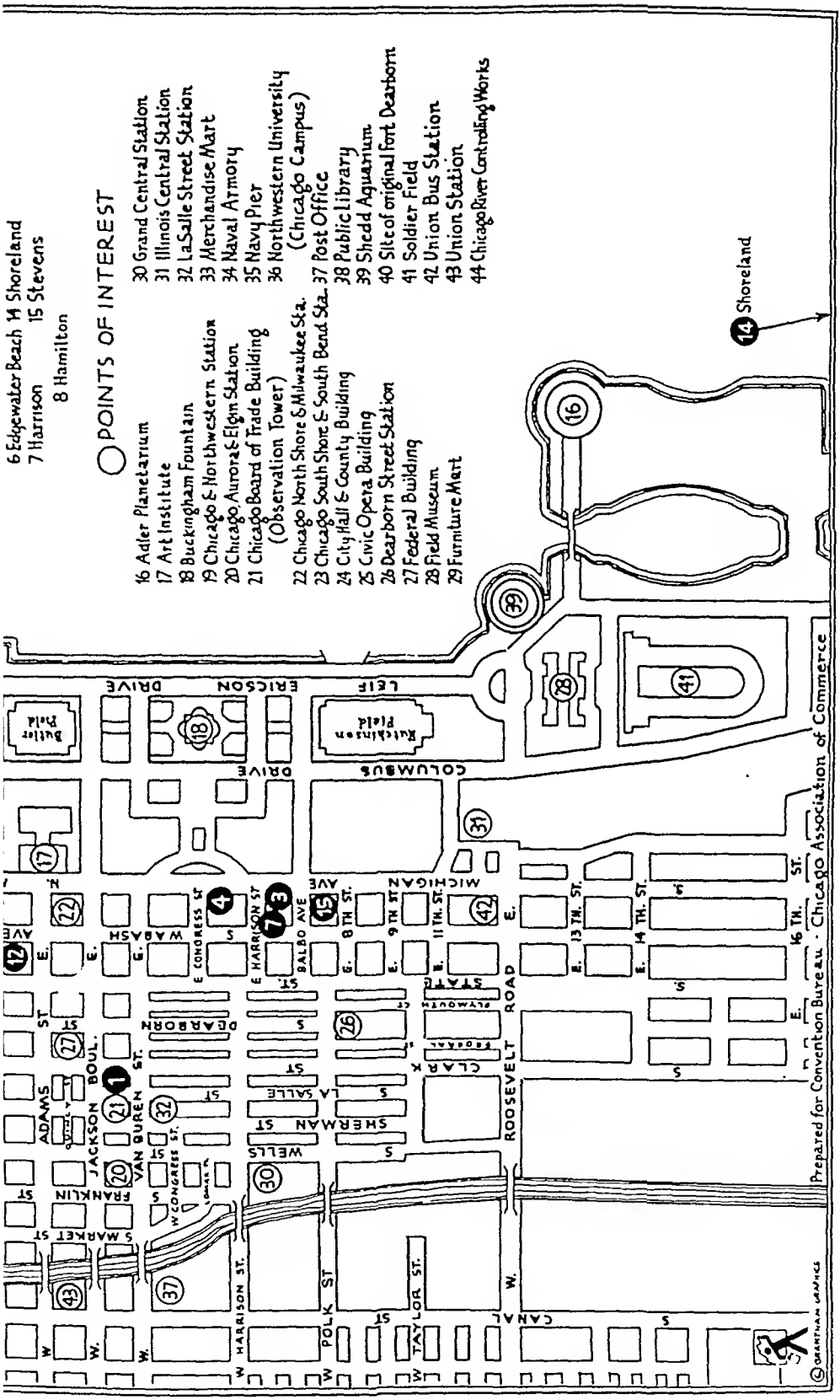
POINTS OF INTEREST
6 Edgewater Beach
7 Harrison
8 Hamilton
14 Shoreland
15 Stevens
16 Adler Planetarium
17 Art Institute
18 Buckingham Fountain
19 Chicago & Northwestern Station
20 Chicago Aurora & Elgin Station
21 Chicago Board of Trade Building (Observation Tower)
22 Chicago North Shore & Milwaukee Sta.
23 Chicago South Shore & South Bend Sta.
24 City Hall & County Building
25 Civic Opera Building
26 Dearborn Street Station
27 Federal Building
28 Field Museum
29 Furniture Mart
30 Grand Central Station
31 Illinois Central Station
32 LaSalle Street Station
33 Merchandise Mart
34 Naval Armory
35 Navy Pier
36 Northwestern University (Chicago Campus)
37 Post Office
38 Public Library
39 Shedd Aquarium
40 Site of original Fort Dearborn
41 Soldier Field
42 Union Bus Station
43 Union Station
44 Chicago River Controlling Works
Butler Field
Buckingham Fountain
Soldier Field
Shoreland
LEIF ERICSON DRIVE
COLUMBUS DRIVE
MICHIGAN AVE
WABASH AVE
DEARBORN ST
CLARK ST
ROOSEVELT ROAD
STATE ST
ADAMS ST
JACKSON BOUL.
VAN BUREN ST
FRANKLIN ST
S. MARKET ST
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Prepared for Convention Bureau - Chicago Association of Commerce

PRELIMINARY PROGRAM

SATURDAY, APRIL 16, 1949

Morning Session

Room 14—9:00 A.M.

Chairman: MERLE MOORE, M.D., Portland, Oregon

Whealing Response of the Skin (Koda slides synchronized with tape recording)

I. The Nature of Skin Whealing with Serial Dilution Testing—*(10 minutes)*

II. Factors Modifying the Whealing Response of the Skin and Their Clinical Importance—*(10 minutes)*

III. The Clinical Use of Serial Testing in the Treatment of Inhalant Allergy—HERBERT J. RINKEL, M.D., Kansas City, Missouri—*(10 minutes)*

Electrophoretic Reaction to Egg White in the Human Skin—S. GROSBERG, M.D., and M. MURRAY PESHKIN, M.D., New York, New York—*(10 minutes)*

Intermission

Intramucosal Tests of the Ocular Conjunctiva (Slides)—HYMAN SHERMAN, M.D., and LOUIS A. FELDMAN, M.D.,* Brooklyn, New York—*(10 minutes)*

A Standardized Patch Test—LOUIS SCHWARTZ, M.D., Washington, D. C.—*(10 minutes)*

Allergic Reactions to Inert Ingredients (Excipients) of Pharmaceuticals—THERON G. RANDOLPH, M.D., Chicago, Illinois—*(10 minutes)*

Lunch

Afternoon Session

Room 14—2:00 P.M.

Chairman: C. B. BOHNER, M.D., Indianapolis, Indiana

An Unusual Allergic Reaction to Penicillin—HARRY LIEBOWITZ, M.D., Brooklyn, New York—*(10 minutes)*

Idioblaptic Tobacco Sensitivity—GRANVILLE F. KNIGHT, M.D., Santa Barbara, California—*(10 minutes)*

Range Oil Fumes as a Cause and Exacerbating Factor in Asthma—ETHAN ALLAN BROWN, M.D., Boston, Massachusetts—*(10 minutes)*

Sensitivity to Kelcoloid (Preliminary Study)—ROY A. OUER, M.D., San Diego, California—*(10 minutes)*

Intermission

Cottonseed Protein vs. Cottonseed Oil Sensitivity

1. Background and Personal Experience—HARRY BERNTON, M.D.,* Washington, D. C.—*(10 minutes)*
2. A Case of Cottonseed Oil Sensitivity—THERON G. RANDOLPH, M.D., Chicago, Illinois—*(5 minutes)*
3. The Atopen Content of Cottonseed Oil—ROBERT S. MCGRATH, M.D., Washington, D. C.—*(5 minutes)*
4. Clinical Experiences—MARY LOVELESS, M.D.,* New York, New York, *(5 minutes)*
5. Results of a Poll Among Allergists—RALPH BOWEN, M.D., Houston, Texas—*(5 minutes)*
6. Intramuscular Injections of Cottonseed Oil in Cottonseed Protein Cases—JOHN H. MITCHELL, M.D., Columbus, Ohio—*(5 minutes)*
7. Present Status of the Problem and Personal Experiences—KARL D. FIGLEY, M.D.,* Toledo, Ohio—*(10 minutes)*

Evening Entertainment

Red Lacquer Room—6:30 to 12:00 P.M.

6:30 p.m. Cocktail Hour

7:30 p.m. Annual Banquet *(Wine, courtesy Marcelle Cosmetics, Inc.)*
Remarks by Retiring President GEORGE E. ROCKWELL, and Newly Elected President JONATHAN FORMAN

8:30 p.m. "Again to the Sea" - Kodachrome Movie with Symphonic Music—HERBERT RINKEL, M.D.

9:30 p.m. - Dancing

PRELIMINARY PROGRAM

SUNDAY, APRIL 17, 1949

Morning Session

Red Lacquer Room—9:00 A.M.

Chairman: F. B. SCHUTZBANK, M.D., Tucson, Arizona

The Application of Psychodynamic Concepts in an Allergy Practice—BENNETT KRATT, M.D., Indianapolis, Indiana—*(20 minutes)*

Emotional Traumata Preceding the Onset of Allergic Symptoms in a Group of Children—HYMAN MILLER, M.D., and DOROTHY W. BARUCH, Ph.D.,* Beverly Hills, California—*(20 minutes)*

A Philosophy of Professional Relationships with Individuals—CARL R. ROGERS, Ph.D.,* Professor of Psychology, University of Chicago—*(30 minutes)*

Intermission

Therapy of Asthma with Special Reference to Its Psychodynamic Pharmacology—HAROLD A. ABRAMSON, M.D., New York, New York—*(20 minutes)*

The Donora Catastrophe—WALTER ROSCAMS, M.D., Donora, Pennsylvania—*(20 minutes)*

Lunch

Afternoon Session

Red Lacquer Room—2:00 P.M.

Pediatric Allergy—Panel under direction of BRIT RAYNER, M.D., New York, New York

1. Genesis of Allergy in Infancy and Early Childhood—BRIT RAYNER, M.D., New York, New York—*(10 minutes)*
2. Antibody Formation in Young Animals—T. N. HARRIS, M.D.,* Philadelphia, Pennsylvania—*(15 minutes)*
3. Evaluation of Diagnostic Tests for Sensitization in Infancy and Childhood—M. MURRAY PESHKIN, M.D., New York, New York—*(15 minutes)*
4. Asthma in Children under Two Years of Age—WILLIAM P. BUFFUM, M.D., Providence, Rhode Island—*(10 minutes)*
5. Hay Fever and Asthma in Children—EDWARD SCOTT O'KEEFE, M.D., Lynn, Massachusetts—*(20 minutes)*
6. Infection in the Allergic Child—BEN F. FEINGOLD, M.D.,* Los Angeles, California—*(15 minutes)*
7. Drug Therapy in Hay Fever and Asthma in Children—JAMES CARNEY OVERALL, M.D.,* Nashville, Tennessee—*(10 minutes)*
8. Urticaria and Eczema in Children—ALBERT V. STOESSER, M.D., Minneapolis, Minnesota—*(15 minutes)*
9. Gastro-Intestinal Allergy in Children—W. AMBROSE MCGEE, M.D.,* Richmond, Virginia—*(10 minutes)*
10. Neurological Allergy in Children—SUSAN COONS DEES, M.D., Durham, North Carolina—*(10 minutes)*
11. Role of Parental Rejection in the Allergic Child—HYMAN MILLER, M.D., and DOROTHY BARUCH, Ph.D.,* Los Angeles, California—*(10 minutes)*
12. Discussion on the Preceding Phases of the Allergic Child—
    RALPH BOWEN, M.D., Houston, Texas—*(5 minutes)*
    ARTHUR J. HORESH, M.D., Cleveland, Ohio—*(5 minutes)*
    RICHARD HENRY TODD, M.D.,* Washington, D. C.—*(5 minutes)*
    JEROME GLASER, M.D., Rochester, New York—*(5 minutes)*
13. Concluding Question and Answer Period.

Discussants will be listed in the final program.

*By invitation.

TO BE READ BY TITLE

Coolweed Extract—Its Use in Poison Ivy—STEPHEN D. LOCKEY, M.D., Lancaster, Pennsylvania

Hepatitis After Pyribenzamine—NATHAN FRANCIS, M.D., Rochester, New York

Aerosol Therapy for Infants and Children—SAMUEL J. PRIGAL, M.D.,* New York, New York

The Use and Abuse of Aerosols in Medical Practice—SAMUEL J. PRIGAL, M.D.,* New York, New York

Respiratory Anaphylaxis—H. N. VERMILYE, M.D., Forest Hills, New York

Possible Sensitization of the Lungs with Phenolsulphonphthalein Aerosols—C. REITER, M.D.,* H. A. ABRAMSON, M.D., B. SKLAROFSKY, A.B.,* and H. H. GEITNER, M.S.,* New York, New York

Bacterial Allergy in Relation to Arthritis—MR. JOSEF HOFFMAN,* Passaic, New Jersey

Tuberculosis and Allergy—ARCHIBALD JUDD, M.D.,* Hamburg, Pennsylvania

The Time Factor and Nebulizer Delivery in Aerosol Therapy—J. B. MILLER, M.D.,* Staten Island, New York

Epinephrine in the Treatment of Migraine—PERRY A. SPERBER, M.D, Providence, Rhode Island

*By invitation.

Technical and Scientific Exhibits

The Exhibition Hall of the Palmer House has been reserved for a Technical and Scientific Exhibit. The exhibits will open at 2 p.m., Thursday, April 14, and will close at 2 p.m., Sunday, April 17. The program has been arranged so there will be a half hour intermission in the morning and afternoon scientific sessions to visit the booths.

Technical Exhibits

Allergen-Proof Encasings, Inc. ..... Cleveland, Ohio
Almay, Inc. ..... New York, N. Y.

Bilhuber-Knoll Corporation ..... Orange, New Jersey
The Borden Company ..... New York, N. Y.

The Chicago Dietetic Supply House, Inc. ..... Chicago, Illinois
Ciba Pharmaceutical Products, Inc. ..... Summit, New Jersey
The Coca-Cola Company ..... Atlanta, Georgia

Dalare Associates ..... Philadelphia, Pennsylvania
The DeVilbiss Company ..... Toledo, Ohio
Ditex Foods, Division of H. W. Walker & Company ..... Chicago, Illinois

Eisele and Company ..... Nashville, Tennessee
Encyclopedia Brittanica, Inc. ..... Chicago, Ill.
Expert Bedding Company ..... Chicago, Illinois

Graham Laboratories ..... Dallas, Texas
L. S. Green Associates ..... New York, N. Y.
Grune & Stratton, Inc. ..... New York, N. Y.

Hoffman-La Roche, Inc. ..... Nutley, New Jersey
Hollister-Stier Laboratories ..... Spokane, Washington

Eli Lilly and Company ..... Indianapolis, Indiana
Luzier's, Inc. ..... Kansas City, Missouri

The Maltine Company ..... Morris Plains, New Jersey
Marcelle Hypo-Allergenic Cosmetics, Inc. ..... Chicago, Illinois
Merck and Company, Inc. ..... Rahway, New Jersey
The Wm. S. Merrell Company ..... Cincinnati, Ohio
C. V. Mosby Company ..... St. Louis, Missouri

Parke, Davis & Company ..... Detroit, Michigan
Philip Morris & Company, Ltd., Inc. ..... New York, N. Y.

Ralston Purina Company ..... St. Louis, Missouri
Rexair Division, Martin-Parry Corporation ..... Toledo, Ohio

Sandoz Chemical Works, Inc. ..... New York, N. Y.
Schering Corporation ..... Bloomfield, New Jersey
G. D. Searle & Company ..... Chicago, Illinois
Sharp and Sharp ..... Everett, Washington
Stemen Laboratories ..... Oklahoma City, Oklahoma

Texas Pharmacal Company ..... San Antonio, Texas

The Upjohn Company ..... Kalamazoo, Michigan

Whittier Laboratories ..... Chicago, Illinois
Winthrop-Stearns, Inc. ..... New York, N. Y.
Wyeth, Inc ..... Philadelphia, Pennsylvania

Scientific Exhibits

Aero-allergens in the National Parks—Mr. Oren C. Durham, Abbott Research Laboratories

Bronchogenic Carcinoma Simulating Other Pulmonary Diseases.—E. R. Levine M.D., Chicago, Illinois

Bronchial Asthma Between the Ages of Fifteen and Fifty-five Years—Its Diagnosis and Treatment in Over 900 Controlled Cases—Albert H. Rowe, M.D., and Albert Rowe, Jr., M.D., Oakland, California

Chemical Relationship of the Antihistamines—M. J. Schiffrin, Ph.D., Hoffman-La Roche, Inc.

Cross-Sensitization to Compounds of Quinone Structure (Aromatic Amines and Azo-Dyes)—R. L. Mayer, M.D., Ciba Pharmaceutical Products

Fungous and Yeast Infections of the Lungs and Bronchi—Abel Froman, M.D., and Frances Whitcomb, M.S., Chicago, Illinois

Graduate and Postgraduate Education in Allergy—Morris A. Kaplan, M.D., and Norman J. Ehrlich, M.D.

Herbarium Committee, American Academy of Allergy.—Mr. Oren C. Durham, *Chairman;* E. P. Claus, A. Orville Dahl; Ralph F. Voight, *Curator.*

How to Overcome Antivivisection Obstructionism—Thomas J. Blakley, National Society for Medical Research

Migraine and Other Allergic Conditions—Leon Unger, M.D., Chicago, Illinois

Mold Allergy—Sidney Friedlander, M.D., Alex S. Friedlander, M.D., and Harold L. Schalter, Detroit, Michigan

Neohetramine: A Pharmacological and Clinical Evaluation—John F. Reinhard, M.D., Nepera Chemical Company, Inc.

Plants of Allergic Importance in the Pacific Southwest—Alfred R. Roos, M.D., and M. Coleman Harris, M.D., College of Medical Evangelists, Los Angeles, California

The Story of the Asthmatic Child—Ralph Bowen, M.D., Houston, Texas

Studies With Steam-Generated Aerosoles—Samuel J. Prigal, M.D., New York, New York

Wheezing—That Is Not Asthma—George L. Waldbott, M.D., Detroit, Michigan

CORRELATION OF EXPERIMENTAL DATA WITH CLINICAL BEHAVIOR OF SYNTHETIC ANTIHISTAMINIC DRUGS

ALEX S. FRIEDLAENDER, M.D., F.A.C.A., and SIDNEY FRIEDLAENDER, M.D.
Detroit, Michigan

IN the last few years a great deal of effort has been expended by chemists and pharmacologists in the development of new antihistaminic drugs. The continued search for newer compounds is based on the hope that some may be found which will more effectively control allergic symptoms and be more readily tolerated by the average patient. Since the entire concept of therapy with antihistamine drugs is based on the theory that histamine plays an integral role in the allergic reaction, the effectiveness of these agents in annulling the pharmacologic actions of histamine in the experimental animal has been a principal determining factor in submitting them for clinical trial. Various techniques to assay this activity have been developed. Some of these methods are open to criticism on the basis that they are far removed from the probable conditions of histamine release occurring in the allergic reaction, and also because of the difficulties involved in attempting to transpose experimental results in animals to the human subject. Inasmuch as there is considerable evidence that histamine is one of the important factors involved in anaphylactic shock of certain animal species, and the role of histamine in allergy is based largely on the belief that the basic mechanism involved in anaphylaxis and allergy are similar, the antianaphylactic action of these synthetic compounds has been suggested as a more accurate guide to their possible effectiveness in human allergy. More recently it has been suggested that the ability of these agents to inhibit experimental whealing in human skin may constitute an excellent method of assaying their clinical potency.[1]

We have had the opportunity of working with a number of these drugs, both in the experimental animal and in patients with allergic disease. Utilizing the same experimental techniques with each drug and employing the same criteria in evaluating clinical effectiveness, it was our opinion that we might be in a position to determine any correlation that might exist between experimental estimations of potency and actual clinical results. We felt it worthwhile therefore to tabulate our experimental and clinical data with six of these drugs; namely, Benadryl, Pyribenzamine, Antistine, Neo Antergan, Neohetramine, and Thenylene (or Histadyl).*

EXPERIMENTAL DATA

Histamine Shock in Guinea Pigs

Materials and Methods.—Protection against fatal histamine shock was

From the Departments of Bacteriology and Medicine, Wayne University College of Medicine, and the Division of Medicine, City of Detroit Receiving Hospital.
Read at the fourth annual session, American College of Allergists, New York, N. Y., March 12, 1948.
* See next page for footnote.

determined quantitatively by two methods: (1) by using a standard protective dose of drug and varying the shocking dose of histamine,[4,5] and (2) by varying the dose of protective drug while keeping the shocking dose of histamine at a constant level.

TABLE I. COMPARATIVE ACTIVITY OF ANTIHISTAMINE DRUGS AGAINST FATAL HISTAMINE SHOCK IN GUINEA PIG

3 Mg./Kg. of Protective Drug (Subcut.)	100% L.D. Histamine Base (Mg./Kg.) I.V.	No. of Lethal Doses Histamine Producing 100% Mortality
Control	0.4	1
Antistine	0.8	2
Benadryl	2.0	5
Antergan	2.4	6
Thenylene or Histadyl	6.0	15
Pyribenzamine	15.0	37
Neo Antergan	50.0	124

Male guinea pigs were used throughout the experiments, intravenous injections being made into the penile veins. All drugs except Neohetramine were compared by the first method, while the six compounds were studied by the second technique. In each instance the antihistamine drug was administered intraperitoneally fifteen to twenty minutes prior to the intravenous shocking dose of histamine. Separate groups of animals, usually averaging ten per group, were used for each change of drug dosage or histamine level.

Results.—

Standard Dose of Drug Against Multiple Lethal Doses of Histamine (Table I).—The 100 per cent lethal dose of intravenous histamine by this technique is 0.4 mg./kg. (calculated in terms of the base). Utilizing a standard dose of 3 mg./kg. of each drug, it was found that 50.0 mg./kg. of histamine, or 124 lethal doses, were required to kill all animals protected with Neo Antergan. Equal amounts of Antistine required two, Benadryl five, Thenylene fifteen and Pyribenzamine thirty-seven lethal doses of histamine to effect 100 per cent mortality.

Varying Amounts of Drug Against One Lethal Dose of Histamine (Table II).—The smallest amount of each drug which protected all animals against 0.4 mg./kg. of histamine was determined. This was found to be 1.0 mg./kg. for Neo Antergan, Pyribenzamine, and Thenylene.

*Benadryl—B-Dimethylaminoethyl benzhydryl ether. Supplied by Parke-Davis and Company, Detroit, Michigan.

Pyribenzamine—N'pyridyl-N'-benzyl-N-dimethylethylenediamine. Supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

Antistine—2-(N-phenyl-N-benzyl-aminomethyl) imidazolin. Supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

Neo Antergan—N-p-methoxybenzyl-N-dimethylaminoethyl a aminopyridine. Supplied by Merck and Company, Rahway, New Jersey.

Neohetramine—2-(N-dimethylaminoethyl-N-p-methoxybenzyl) aminopyrimidine. Supplied by Nepera Chemical Company, Yonkers, N. Y.

Thenylene—(a-pyridyl)-N-(a-thenyl)-N', N'dimethylethylenediamine. Supplied by Abbott Laboratories, North Chicago, Illinois. Histadyl is the same drug manufactured by Eli Lilly and Company, Indianapolis, Indiana.

TABLE II. COMPARATIVE PROTECTION AGAINST ONE LETHAL DOSE OF HISTAMINE (0.4 MG/KG)

Mg./Kg. of Protective Drug	Neo Antergan		Pyribenzamine		Thenylene		Benadryl		Neohetramine		Antistine	
	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality
0.1	9/4	44	10/6	60	10/6	60						
0.5	10/1	10	10/5	50	10/4	40						
1.0	10/0	0	10/0	0	15/0	0			8/4	50		
2.0												
3.0	10/0	0	10/0	0			10/3	30	10/6	60	10/3	30
5.0							10/0	0	10/0	0	10/2	20
8.0											10/2	20
10.0											10/0	0

TABLE III. PROTECTIVE ACTION OF BENADRYL AND PYRIBENZAMINE AGAINST GUINEA PIG ANAPHYLAXIS

Mg./Kg. Protective Drug	Control		Benadryl		Pyribenzamine	
	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality
None	12/11	91				
1.0			10/5	50	10/6	60
2.0			10/3	30	10/3	30
3.0			10/0	0	10/0	0

Comparative mortality figures with smaller amounts of each drug show the protective power of Neo Antergan to be somewhat greater than either Pyribenzamine or Thenylene. Benadryl, Neohetramine, and Antistine prove less effective than the other three drugs, with 5 mg./kg. of Benadryl and Neohetramine and 10 mg./kg. of Antistine being required for complete protection. While the variations between drugs is not nearly as great, the order of efficacy in this experiment is essentially the same as determined by the multiple lethal dose method.

Guinea Pig Anaphylaxis

Materials and Methods.—Three series of anaphylactic experiments were carried out. The antianaphylactic effect of two drugs was compared in each series. In the first group, animals of uniform weight (300 to 400 gm.) were passively sensitized by the subcutaneous injection of 0.5 c.c. of rabbit antihorse serum, and forty-eight hours later were given an intravenous injection of 1 c.c. of horse serum in the penile veins. Varying doses of Benadryl and Pyribenzamine were administered intraperitoneally fifteen to twenty minutes prior to the shocking dose of antigen and results compared with appropriate controls. In the second and third series, guinea pigs (400 to 500 gm.) were actively sensitized by the subcutaneous injection of 0.1 c.c. of horse serum, and given 0.5 c.c. intravenously fourteen days later. The protective action of Thenylene and Neohetramine were compared in the second group, while Antistine and Neo Antergan

TABLE IV. PROTECTIVE ACTION OF THENYLENE AND NEOHETRAMINE AGAINST GUINEA PIG ANAPHYLAXIS

Mg./Kg. Protective Drug	Control		Thenylene		Neohetramine	
	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality
None	14/14	100				
0.01			10/10	100		
0.1			14/6	43	10/10	100
1.0			10/2	20	10/6	60
3.0			10/0	0	10/3	30

TABLE V. PROTECTIVE ACTION OF ANTISTINE AND NEO ANTERGAN AGAINST GUINEA PIG ANAPHYLAXIS

Mg./Kg. Protective Drug	Control		Neo Antergan		Antistine	
	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality	No. Used / No. Died	% Mortality
None	10/10	100				
0.1			10/5	50		
1.0			10/2	20	10/8	80
3.0			10/0	0	10/6	60
5.0					10/2	20

were compared in the third series of animals. In each instance the protective compound was injected fifteen to twenty minutes before intravenous dose of antigen.

Results.—

Benadryl and Pyribenzamine (Table III).—Eleven of twelve control animals died in typical anaphylactic shock. All animals survived when protected with 3.0 mg./kg. of either Benadryl or Pyribenzamine. Smaller amounts of each drug appeared to confer an equal amount of protection. Within the limits of this experiment there appeared to be no essential difference between the protective power of Benadryl and Pyribenzamine.[4]

Thenylene and Neohetramine (Table IV).—All control animals died in typical anaphylactic shock. Animals given 3.0 mg./kg. of Thenylene were protected against fatal shock, while a similar amount of Neohetramine protected seven of ten animals. At 1.0 mg./kg, eight out of ten Thenylene-treated animals survived, as compared to four out of ten who were given Neohetramine. All animals who received 0.1 mg./kg. of Neohetramine died, while the same amount of Thenylene protected 57 per cent of the animals. The results of this experiment indicate a greater degree of protection against anaphylaxis on the part of Thenylene.

Antistine and Neo Antergan (Table V).—All control animals promptly died in anaphylactic shock. Neo Antergan appeared to be considerably more effective than Antistine against anaphylaxis. Mortality was absent in

animals receiving 3.0 mg./kg. of Neo Antergan, while the same amount of Antistine protected only four out of ten guinea pigs. At 1.0 mg./kg., 80 per cent of Neo Antergan-treated animals survived as compared to 20 per cent of those receiving Antistine.

TABLE VI. ANTI-WHEALING EFFECT OF ANTIHISTAMINE DRUGS

Serial Dilutions of Drugs against Standard Histamine Wheal

Drug	Average Conc. (Mg./c.c.) to Produce 50 Per Cent Inhibition
Neo Antergan	0.5
Thenylene (Histadyl)	0.5 to 1.0
Pyribenzamine	1.0
Benadryl	1.0
Neohetramine	5.0
Antistine	10.0

Histamine Wheals in the Human Skin

Early studies of antihistamine agents revealed their effectiveness in reducing the "triple response" ordinarily induced in the human skin by histamine.[3] Further investigation showed that the allergic wheal, as well as whealing produced by venoms or irritant chemical substances, was likewise affected by the antihistamine drugs.[6]

Materials and Methods.—The relative effectiveness of the six drugs in reducing the whealing response of the human skin to histamine was determined. All drugs were tested simultaneously on the back of each subject so that closer comparisons could be made. The procedure outlined in an earlier report was followed; namely, that of first treating a scratch site with the test drug for ten minutes, followed by the application of histamine to the same site. Reactions were recorded ten minutes after the application of histamine. Two general methods of assay were employed; (1) where individual scratches were treated with serial dilutions of the drug (0.1 to 50.0 mg./c.c.), and later tested with a standard amount of histamine previously determined to produce a maximal wheal in that subject (usually 1:1,000 or 1:2,000); and (2) where scratches were treated with solutions of drug containing 1 mg./c.c., and later tested with serial dilutions of histamine (1:1,000 to 1:32,000). Comparisons with controls were made in each instance.

Results.—

Serial Dilutions of Drugs Against Standard Histamine Wheal (Table VI).—This study was carried out in ten subjects. The whealing reactions were reduced most effectively in the majority of instances at Neo Antergan-treated sites. Thenylene, Pyribenzamine, and Benadryl were approximately equal in their antiwhealing action, while Neohetramine and Antistine proved less effective. An estimation based on the amount of drug applied to a

scratch site which resulted in at least a 50 per cent inhibition of the whealing reaction would show Neo Antergan the most effective, Thenylene, Pyribenzamine and Benadryl next, followed by Neohetramine and then Antistine.

Standard Amount of Drug Against Serial Dilutions of Histamine.—A comparison of the inhibitory action of each drug in this type of study showed Neo Antergan to be the most effective antagonist of histamine whealing in eight of ten subjects. In one instance Pyribenzamine was most effective, and in another, Thenylene displayed the greatest action. Both these drugs were approximately equivalent in their antiwhealing effect and only slightly less active than Neo Antergan. Benadryl was next in order of effectiveness, followed by Neohetramine, while Antistine again displayed the weakest action of the six drugs.

CLINICAL COMPARISON

Data has been accumulated covering the clinical use of each of these drugs in over 100 patients.

Dosage and Toxicity.—An important factor limiting the use of antihistamine drugs in many patients is the frequent occurrence of unpleasant side actions. While a great variety of side effects have been noted, drowsiness appears to be the most common untoward action encountered with all drugs. Vertigo, nervousness, weakness, and gastrointestinal irritation are probably next in order of frequency. No serious toxic reactions have been observed with any of the drugs studied. The incidence of side effects varies from one compound to another, as well as from one individual to another. Those unable to tolerate one drug are frequently able to take an effective dose of another without difficulty. In our clinical evaluation of these compounds we have usually prescribed initial doses of 50 mg. In the absence of clinical response and untoward side effects the dose was increased to 100 mg. Where 50 mg. doses proved helpful it was found in some instances that smaller amounts were sufficient to control symptoms. The effect of an oral dose is usually evident within thirty minutes and lasts several hours. Continuous symptoms usually require three or four doses during the twenty-four-hour period, and at times more frequent administration is necessary. There is little clinical evidence at this time to indicate that the duration of action of one drug is longer than that of another.

Taking into consideration the incidence of side effects encountered with each drug, we found that the optimum dosage of Benadryl, Pyribenzamine, Neo Antergan, and Thenylene was 50 mg., while that of Neohetramine and Antistine was 100 mg. Employing the optimum dosage in most cases, side effects from Benadryl occurred in 34.04 per cent, from Pyribenzamine in 27.2 per cent; from Thenylene in 24.56 per cent; from Antistine in 23

TABLE VII. CLINICAL RESULTS WITH SOME NEWER ANTIHISTAMINE DRUGS

Condition	Neo Antergan		Neohetramine		Thenylene or Histadyl		Antistine	
	No. of Cases	% Helped	No. of Cases	% Helped	No. of Cases	% Helped	No. of Cases	% Helped
Rhinitis (Nonseasonal)	41	58	50	32	50	64	59	59
Rhinitis (Seasonal)	41	70	58	62	40	75		
Asthma	17	29	40	27	21	33	24	37
Dermatitis								
Atopic	3	33	3	0	2	50	5	60
Contact	0	0	2	50	5	80	6	50
Unclassified	5	60	4	75	2	0		
Urticaria								
Acute	4	75	6	100	5	80	10	70
Chronic	5	100	4	50	9	77	9	33
"Serum-Sickness"	4	100					1	0
Headache, Allergic	4	25	3	0	2	0	6	16
Conjunctivitis	2	0	1	0				
Pruritus Ani					1	0	1	0

per cent in one group and in 18.05 per cent in another; from Neo Antergan in 21.9 per cent, and from Neohetramine in only 12.14 per cent. The low incidence of side action with Neohetramine frequently permitted its use in patients who were particularly prone to experience difficulty from other antihistaminics. At times the side effect of drowsiness may be a desirable attribute of antiallergic medication. It is not uncommon for us to prescribe a well-tolerated drug during the day, and employ another with a high index of drowsiness at bedtime. The sedative action is frequently helpful in certain cases of urticaria and pruritic dermatitis.

Symptomatic Effect (Table VII).—One of the striking features which becomes apparent when clinical efficacy is compared is that all drugs are relatively helpful in controlling certain allergic symptoms and of comparatively little value in affecting others. All the drugs under discussion show their greatest effect in the control of urticaria and angioneurotic edema, and in the acute symptoms of seasonal hay fever. They appear to be somewhat less effective in perennial allergic rhinitis and in the relief of pruritus. Their action in asthma is inconstant and generally disappointing. The effect on the irritating asthmatic cough, especially in children, is usually more gratifying than on wheezing dyspnea.

In comparing the incidence of improvement obtained in various allergic syndromes, we find that the results with each drug are quite similar. The small differences in figures are hardly significant in view of the many variable factors influencing the allergic state. Yet, by the use of several drugs in the same patient one is able at times to decide, both from the patient's own opinion in the matter and from objective evidence, that one drug is more effective in that individual than another. We gain the impression from the use of these drugs in optimum dosage that a greater degree of symptomatic relief is more often obtained with Pyribenzamine,

Neo Antergan, and Thenylene. Nevertheless, we have encountered many patients who obtained superior results from Benadryl, Neohetramine, or Antistine. There is indeed a wide individual variation in the response to these drugs, and having a number of them at our disposal enhances the possibility of finding one which will be most suitable for that particular patient.

DISCUSSION

The rather marked differences in antihistamine effect which are present when the multiple lethal dose method of assay is used become much less evident when the drugs are compared against the fatal effects of a single lethal dose of histamine. The order of efficacy of the various compounds, however, is essentially the same in both methods. In comparing the antianaphylactic behavior of a drug with relatively higher antihistaminic activity against one with a lower index, differences were evident in two out of three series of experiments corresponding to the variations observed against one lethal dose of histamine. These results would support the contention that antianaphylactic activity is related to antihistaminic activity. In their action on histamine wheals in the human skin, differences between drugs are observed which follow essentially the same order seen in guinea pig experiments. It might be of greater interest in this respect to determine whether the same tendency is shown against experimental allergic wheals.

Variations in the clinical effectiveness of these drugs, while not as clear cut as those shown in experimental studies, also follow the same general pattern. For instance, Antistine and Neohetramine usually require 100 mg. doses to produce clinical effects comparable to those produced by 50 mg. doses of Pyribenzamine or Neo Antergan. Quantitative differences shown experimentally, however, are not identical in clinical experience. One compound which proves itself several times more active than another is usually not of increased clinical effectiveness in the same proportion. There are also instances where a patient will respond more favorably to an equivalent amount of a generally less active drug. In general, however, the differences these drugs exhibit in clinical allergy tend to parallel the variations observed in histamine shock, guinea pig anaphylaxis, and experimental whealing.

SUMMARY

1. Six antihistamine drugs, Benadryl, Pyribenzamine, Antistine, Neo Antergan, Neohetramine, and Thenylene (Histadyl) were compared experimentally and clinically to determine any correlations which might exist.

2. In guinea pigs, wide differences in antihistaminic activity were noted when the drugs were compared on the basis of protective action against multiple lethal doses of histamine. Less variation was apparent when com-

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WHALE OIL, TRICHOPHYTIN, AND AUTOSEROTHERAPY IN THE TREATMENT OF EPIDERMOPHYTOSIS

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DURING my service at Fort Devens, Massachusetts, in 1935-1936, I became deeply impressed by the marked prevalence of epidermophytosis and the lack of a good therapeutic agent with which to treat the disease. Research with various oils was undertaken, and a chance remark by a whaling captain, that none of his crew suffered from athlete's foot, suggested that whale oil might be worthy of investigation as a method of treatment for fungus infections.

Before beginning a discussion of whale oil, it seems appropriate to review briefly the subject of epidermophytosis and its therapy.

GENERAL NATURE AND CLASSIFICATION OF EPIDERMOPHYTOSIS

This paper is concerned only with the lesions produced by the fungi that are limited to the superficial horny layers of the epidermis. In the United States the common species of infecting fungi are (1) Trichophyton interdigitale (synonyms: T. mentagrophytes, T. gypseum), (2) Trichophyton purpureum (synonyms: T. Rubrum, Epidermophyton rubrum), and (3) Epidermophyton inguinale. Dodge[6] classifies the lesions of the horny layer on the basis of the dry portions, moist (interdigital) and very thick layers (palmar and plantar) of the skin:

Dry—(a) dry and scaling; (b) vesiculose
Moist—(a) eczema marginatum; (b) dysidrosiform or hyperkeratotic
Thick—(a) dysidrosiform or hyperkaratotic

As to the prevalence of the types, Beckjord[2] describes how he examined a group of engineers, 40 per cent of whom were infected, and classified them as 30 per cent vesicular, 60 per cent intertriginous and 10 per cent hyperkeratotic.

The fungi can only grow in the horny layers of the epidermis, multiplying and producing lesions, although they can survive in internal organs and travel in the blood stream. The production of metabolites in the skin or internal organs causes allergy. As a result of these altered reactions, precipitins, agglutinins and complement fixation antibodies appear.

There also appears to be an antibody which checks the growth of the fungus and thereby helps in the healing processes. These allergic manifestations produce the characteristic lesions, trichophytids or epidermophytids. Their appearance is due to the transmission of metabolites. Generalized symptoms and various skin manifestations may ensue.

It should be born in mind that dermatophytes are not exclusively the etiological agent in athlete's foot. Hopkins[9] showed that in 30 per cent of

military personnel he could not detect fungi in the intertrigos of the toes. Some of these nonmycotic lesions were due to staphylococcus aureus reactions, shoe polish, antiseptics, fungicides or other sensitizing agents. Trauma and hypostasis are the cause in some cases. The majority are, however, the result of fungus infection with improper foot hygiene as the prominent predisposing cause.

THERAPEUTICS

There have been two types of experimentation in an effort to find a cure—*in vivo* and *in vitro*. The latter has often failed because the fungi behave differently in the human skin than in culture media.

Owing to the difficulty of securing penetration into the horny layer of the skin, the usual antiseptics are useless. By the application of keratolytics, we may peel off one layer faster than the fungus can penetrate the next. This also is of value in bringing a fungicide in contact with the fungus, which may be covered over by some horny layers of the epidermis.[1]

Among the fungicidal agents used are iodine, mercury salts, thymol, salicylic and benzoic acids, formaldehyde, dyes such as crystal violet, gentian green, gentian violet, neutral red and others. Kingery and Adkisson used many volatile oils. They showed that aqueous solutions of thymol, cinnamon and eugenol were superior to the others in the order named, for restraining growth on agar. Recently newer fungicides have come forward, such as undecylenic acid,[20] propionates,[11] and sodium caprylate.[12]

Physical agents have been used such as x-rays and ultraviolet therapy. Among the miscellaneous items have been vitamins, cod liver oil and sulfonamide drugs, among which sulfonilamide[5] alone had value.

The biological approach utilizes fungus extracts such as trichophytin. Some workers are pleased by their results with trichophytin, while others feel it is valueless.[1,16]

WHALE OILS

Whale oil is extracted from the blubber of different species of the genus Baloena such as Baloena mysticetus (Greenland or Right whale), Baloenoptera hyperoödon (Bottle Nose whale), and Baloenoptera Sibbaldi (Blue whale). There are also others like the Killer whale, the White whale and the Sulfur Bottom whale. Table I shows the variations in physical and chemical properties.[7,13,15]

Milligan, Knuth and Richardson report an analysis of whale oil fatty acids as follows: Myristic 4.5%, Palmitic 11.5%, Palmitoleic 17.0%, Stearic 2.5%, Oleic 36.5%, C unsaturated 16%, C unsaturated 10%, C unsaturated 1.5%. Myddleton and Barry report the analysis of fatty acids shown in Table II.

Buttenberg and Angerhausen state that the unsaponifiable matter of whale oil, after removal of cholesterol, is optically active in contradistinction to that of other animal fats. Whale oils, when crystallized from

TABLE I

	Specific Gravity at 15° C.	Acid Value	Sapon. Value	Iodine Value	Unsapon. Matter
Antarctic Right Whale oil (America)	0.9257	0.56	183.1	136.0	1.46
Whale Oil No. 1, unrefined (Finmarken)	0.9181	0.86	188.6	104.0	2.36
Refined (Glasgow)	0.9214	1.4	184.7	113.2	2.33
Arctic whale oil, refined (America)	0.9234	1.9	185.0	117.4	2.11
Crude white whale oil (America)	0.9222	2.5	183.9	127.4	1.37
Whale oil No. 2, unrefined (Finmarken)	0.9182	3.6	188.3	——	3.3
Yellow whale oil, unrefined (Glasgow)	0.9232	10.6	185.9	110.0	1.89
Whale oil No. 3, unrefined (Finmarken)	0.9162	26.5	185.7	96.0	2.42
Brown whale oil, refined (Glasgow)	0.9272	37.2	160.0	125.3	3.22
Whale oil No. 4, unrefined (Finmarken)	0.9205	58.1	182.1	89.0	3.4
Dark whale oil, refined (Glasgow)	0.9170	98.5	178.3	103.1	3.03

TABLE II

	Newfoundland Whale	South Sea Whale
Myristic	9	8
Palmitic	10	12
Linoleic	9	20
Stearic	3	—
Oleic	35	25
Palmitoleic	18	17
Arachidonic	16	—
C H O	—	18

TABLE III

	Whale	Sperm	Cod Liver
Specific gravity at 15° C.	.920-927	.878-.883	.926-927
Saponification value	180-197	125-140	183-188
Mod. value	1.4630	1.4580	1.4705
Iodine value	105-35	80-90	160-170
Titre of fatty acids 0° C.	22-25	———	14-25

acetone, yield a larger quantity of insoluble glycerides. As with all oils, however, a large proportion of the constituents are unknown.

Sperm oil, derived from the sperm whale, differs from all other whale oils in that it is a liquid wax. The latter contain no glycerides, consisting chiefly of compound esters of fatty acids and monovalent alcohols. They therefore yield large quantities of unsaponifiable matter on saponification.

Table III lists the differences between whale, sperm and cod liver oils.

TREATMENT OF EPIDERMOPHYTOSIS WITH WHALE OIL

Experimentation was begun with the crude variety of the Right whale (Baloena Mysticetus). This oil was a pale yellow and very fishy in odor. Results were astounding. Itching, scaling and cracking of the skin disappeared. Healing was very rapid. On the severer types of tinea of the feet and also in cases refractive to ordinary therapy, results were just as gratifying.

The objectionable feature of the crude variety was the odor. It was then decided to try the refined whale oil. This is an amber color. All

treatments have since been given with this oil. No detectable differences in results were seen in the usage of refined over crude whale oil.

It was next decided to see whether sperm oil might prove better than the Right whale type. As has been stated before, this is a liquid wax and not a fixed or fatty oil. In the cases that were under treatment with blubber Right whale oil, the sperm was substituted. The patients either remained stationary or relapsed. In cases that were treated initially with sperm only, no progress was made, showing that sperm oil has no specific action against epidermophytosis.

A highly refined sperm wax of white color and entirely free of fish odor was also tried and found to be valueless.

THERAPEUTIC CLASSIFICATION OF EPIDERMOPHYTOSIS BASED UPON THERAPY WITH WHALE OIL

As a result of experience this workable classification of trichophytosis has been devised for the treatment of athlete's foot. Location is not of prime importance, but the severity of the disease is.

Mild.—Characterized by slight itching, mild dermatitis, minor cracking and peeling of skin. Treatment: Daily swabbing of areas with whale oil. Itching disappears quickly, and recession of the dermatitis is very rapid. Treatment for a month after all symptoms are gone is advocated.

Moderately Severe.—Characterized by moderate itching, more marked dermatitis with cracking and deep ulcerations, increase in amount of macerations, vesicles, and necrosis of tissue. Treatment: Cleaning off of macerated skin, opening and drainage of vesicles, removal of necrotic scales and tissue. After the above has been carried out (and this is very important in success of treatment), then the entire area is swabbed, and pledgets of cotton saturated in the oil are applied or bandaged to the parts.

Severe.—Characterized by intense itching, severe dermatitis, vesicles of bullae, marked necrosis. Treatment: Blebs or bullae are opened and drained. Necrotic tissue is trimmed off daily. Swabbing of entire area, and continuous wet dressings with whale oil.

Most of our clinical research has been carried out on the moderately severe and severe types. It is very important to have the oil in direct contact with the living diseased tissue and not with necrotic skin.

Whale oil penetrates dead tissue and stains it yellow, while the living remains practically untouched as regards color. Scales, macerations, and desquamations are yellow. This enables us to know what portions are nonviable and so we remove them at each treatment. Unless this important point is emphasized, we only delay healing by failing to treat the actively diseased area.

LABORATORY TESTING OF WHALE OIL

As a result of the clinical effectiveness of whale oil, it was decided to submit it to laboratory testing. The following reports are offered as to

TABLE IV

Number	Organism	Phenol. Resistance*
1.	*Trichophyton mentagrophytes* (Harvard No. 60)	1:80-1:90
2.	*Trichophyton mentogrophytes* (Emmon's strain; ATCC No. 9533)†	1:45-1:50
3.	*Epidermophyton interdigitale* (Weidman's strain; ATCC No. 2371)	1:80
4.	*Achorion quinckeanum* (ATCC No. 644)	1:20-1:30
5.	*Trichophyton purpureum* (Emmon's strain; ATCC No. 9806)	1:70
6.	*Epidermophyton rubrum* (Weidman's strain; ATCC No. 4183)	1:90-1:100
7.	*Trichopyton tonsurans* (Emmon's strain; ATCC No. 9194)	1:70-1:80
8.	*Trichophyton accuminotum* (Emmon's strain; ATCC No. 9292)	1:90
9.	*Achorion schoenleinii* (Weidman's strain; ATCC No. 4822)	1:90-1:100
10.	*Trichophyton violaceum* (Emmon's strain; ATCC No. 8376)	1:80-1:90
11.	*Microsporon canis* (Emmon's strain; ATCC No. 9084)	1:130
12.	*Microsporon felineum* (NCTC No. 3006)†	1:90-1:100
13.	*Epidermophyton floccosum* (Emmon's strain; ATCC No. 9646)	1:70-1:80
14.	*Epidermophyton inguinale* (R No. 285)	1:100
15.	*Monilia albicans* (ATCC No. 2091)	1:50-1:60
16.	*Microsporon audouini* (Emmon's strain; ATCC No. 9082)	1:120

*Phenol resistance is the highest dilution of phenol which kills the test organism in ten minutes at 20° C.
†ATCC = American Type Culture Collection.
NCTC = National Collection of Type Cultures (England).

the tests performed. The organisms selected for the study, along with their respective phenol resistances, are shown in Table IV. Fungicidal activity was determined by the method of Burlingame and Reddish.[4]

The results of this test with all organisms, both in the presence and absence of 10 per cent human serum, showed growth after exposure of the mycelial mat to the oil for the maximum period of the test, 120 minutes. The action of the oil is, therefore, not fungicidal. A test which will demonstrate bacteriostatic activity of the oil was indicated. The method selected was that of Ruehle and Brewer.[19] The average results of quadruplicate platings for each organism are given in Table V.

In summary, the results indicate that Right whale oil is nonfungicidal, but does exert a decided inhibitory effect on the germination of the conidia and the growth of the mycelium of the pathogenic fungi examined. The fungistatic activity is even more striking in view of the fact that the results of the test depend as much upon penetration or diffusion of the active material through the culture medium as it depends upon restraint of growth. Here we are dealing with an oil, the diffusion of which, through an aqueous medium, is, from all indications, very limited and slow. The magnitude of the zone observed suggests that the oil contains a water-miscible substance which may be responsible for the effect we have observed as the activity of the whale oil.

Methods were used to try and determine the exact nature of the active material. Neither hot nor cold water extraction tests could isolate the active

TABLE V

Number	Organism	Zone of Inhibition* in millimeters after an incubation period of 3 days	5 days	10 days
1.	*Trichophyton mentagrophytes* (Harvard No. 60)	8	4	0
2.	*Trichophyton mentagrophytes* (Emmon's strain; ATCC No. 9533)	7	2	0
3.	*Epidermophyton interdigitale* (Weidman's strain; ATCC No. 9533	8	5	0
4.	*Achorion quinckeanum* (ATCC No. 644)	12	7	1
5.	*Trichophyton purpureum* (Emmon's strain; ATCC No. 9806)	7	2	0
6.	*Epidermophyton rubrum* (Weidman's strain; ATCC No. 4183)	10	5	0
7.	*Trichophyton tonsurans* (Emmon's strain; ATCC No. 9194)	8	6	0
8.	*Trichophyton accuminatum* (Emmon's strain; ATCC No. 9292)	10	4	1
9.	*Achorion schoenleinii* (Weidman's strain; ATCC No. 4822)	7	6	1
10.	*Trichophyton violaceum* (Emmon's strain; ATCC No. 8376)	13	10	3
11.	*Microsporon canis* (Emmon's strain; ATCC No. 9084)	13	10	3
12.	*Microsporon felineum* (NCTC No. 3006)	11	5	1
13.	*Epidermophyton, floccosum* (Emmon's strain; ATCC No. 9646)	8	5	0
14.	*Epidermophyton inguinale* (R No. 285)	8	5	0
15.	*Monilia albicans* (ATCC No. 2091)	7	5	0
16.	*Microsporon audouini* (Emmon's strain; ATCC No. 9082)	10	7	1

*Width of clear zone, i.e., zone free from growth, measures from edge of mycelium to rim of cup, averaged to nearest millimeter.

ingredient. Our feeling is that there is a chemical or physical binding of the unknown material with the oil or nonlipid compounds in the Right whale oil. This complex then dissociates under specific but unknown conditions. Research is continuing in the hope of isolating this substance.

It is evident from the laboratory investigations made that the oil exhibits marked fungistatic properties against all fungi tested. Since three varieties are responsible for most of the cases of epidermophytosis, i.e., T. interdigitale, T. purpureum and Epidermophyton inguinale, we have a powerful inhibitory mechanism to check their growth. With normal defensive and recuperative body forces we are in position to achieve clinical cures, for we can check the growth of both mycelia and the conidia, thus allowing nature to overcome the static forms.

DISCUSSION

The results corroborate the laboratory findings. In the mild classification type, clinical cures are almost 100 per cent. In the severe and moderately severe cases the percentages vary from 80 per cent to 90 per cent, depending on different series. In three series of moderately severe cases, results were as follows:

131 cases (age groups 16 to 22) .....15 failures—12% failures
C.C.C. and military personnel.
87 cases (age groups 12 to 50) .....13 failures—15% failures
Civilians.
107 cases (age groups 10 to 47) .....18 failures—17% failures
Civilians.

325 cases .....46 failures—14% failures

In the severe type, results were as follows:

63 cases	(age groups 16 to 25) C.C.C. and military personnel.	11 failures—18% failures
47 cases	(age groups 15 to 38) Civilians.	10 failures—21% failures
21 cases	(age groups 17 to 31) Civilians.	6 failures—28% failures
131 cases		27 failures—21% failures

Cases have been studied for eleven years, and while all have not been fully tabulated, they total several thousand. The majority which I have seen are naturally the mild type. I speak only of clinical cures because there is no way of knowing when the fungi have been completely eliminated from the integument. Reinfection from improper foot hygiene and prophylactic measures must be taken into account. It is difficult, too, to have patients continue treatment after skin lesions have apparently healed. Mycotic elements may still be present and over-treatment with the oil is paramount. In dealing with this bland material we can do no harm.

The percentage of failures in my hands, under intensive therapy, has been small, ranging approximately from 10 to 20 per cent. In the moderately severe and severe classified types, better results are attained by having the physician treat the patient, or, if not possible, by having him return at short intervals for supervision. Macerations and scales should be removed. Vesicles and bullae must be opened and all possible necrotic skin should be excised at each sitting. Dead skin stains yellow and thus serves as a guide for removal. It must be stressed that only when whale oil is in direct contact with the living infected skin, can we expect results.

The causes for failures secured with whale oil can be readily analyzed and remedied. If we can rule out improper application of the medication, we may assume that we have not reached the fungi. A keratolytic may be indicated to peel off more epidermis so as to bring the mycotic elements into direct contact. After adequate desquamation, whale oil can again be applied.

A second reason for failure may be poor local tissue resistance. High local resistance or low invading virulence should be manifest by the mild type of disease. Moderately severe or severe classified types would indicate fair or poor local defensive power or higher invading virulence. A bland fungistatic agent should be of more value in these cases than a strong fungicide which will injure the skin and further break down local resistance. Normally, the dermal organ is a good producer of antibodies. It is logical to assume that antimycotic ones are formed to combat infection. If they are present in sufficient quantity, healing should take place, but if lacking, the disease will continue. In summary, the degree of infection is predicated upon local defensive power, which probably depends upon high enzymatic resistance and sufficient antibody production.

A third reason for failure is the presence of an allergic phenomenon. Treatment of dermatophytids, which are allergic in scope and contain no

infecting elements, will fail. The primary infected tissue should be treated. Clinically, whale oil is a good test to differentiate the so called "ids."

IMMUNOTHERAPY AS AN ADJUNCT TO WHALE OIL THERAPY

The percentage of clinical cures with whale oil is high. The thought naturally occurred as to how we might increase the percentage of clinical cures and treat the failures of whale oil therapy. Where we have failed to reach the fungus, a keratolytic may be used and whale oil again applied. For this we have used Whitfield's ointment. Sometimes this alone may be sufficient to secure results. Again it should be emphasized that the primary focus or foci should be treated.

The other reasons for failures may be considered all together, as they involve basic principle in immunology and allergy. When foreign agents invade the body, the organism may become (1) injured or destroyed, or if it survives it may become (2) allergic or (3) immune.[18]

In the allergic individual there are cellular antibodies occurring in the tissues alone. In the immune person, antibodies are produced in greater quantities and appear in the blood stream, neutralizing antigens before they reach the antibody-containing cells. It is thus conceived that allergy precedes a state of immunity. However, immunity is not a static condition, and a person immune at one time may again become allergic, or the reverse may hold true.

The dermal organ is a good producer of antibodies, in fact it manufactures antibodies in greater number and more rapidly than any other organ. It is generally accepted that intense specific stimulation of the skin is sufficient to protect the entire organism. Intradermal injections of antigens elicit greater antibody response than subcutaneous inoculations, especially with much smaller doses.

Hypersensitiveness of the integument is encountered mostly in the deep inflammatory mycoses, although it may be present in superficial chronic lesions. According to Jadassohn, when allergy is strongly present, the fungi may be quickly destroyed. When it is of moderate intensity it merely inhibits the hyphomycetes so that the growth may again progress as soon as local immunity subsides. Bloch[3] has shown in both animals and humans that once an individual recovers from a fungous disease, the entire skin surface, including areas that were not clinically infected, acquires a state of allergy, as evidenced by a more rapid and less intense reaction to infection. Skin lesions heal because of locally developed immunity.

Mycotic allergy may be explained on the usual immunological basis of cellular and humoral antibodies. Martenstein[14] was able to demonstrate specific antibodies in the skin of guinea pigs sensitized to a fungus. Jessner and Hoffman[10] found the blood of patients with trichophytosis inhibited the growth of fungi. Sulzberger[21] and Kerr showed by passive transfer methods, the presence of an antibody to trichophytin. This was confirmed later by Tomlinson[22] and Henrici.[8] Extracts of Trichophytin, Microsporin,

Epidermophytin and Favin can be used to demonstrate skin allergy as regards their particular fungi. The trichophytin test represents a group reaction in the majority of cases for it is also positive in microsporic and epidermophytic infections. Sulzberger says that the hyphomycetes contain, in addition to the allergenic factors that are specific for each species, an allergic principle common to all.

Trichophytin is both a diagnostic extract and an immunizing agent. Intradermal testing may be done with dilutions of 1:30 up to 1:500. Personally, I prefer to start with dilutions of 1:100,000 (in cases suspected of marked allergy), and if negative, use serial dilutions of 1:10,000 contining to 1:100, stopping whenever a positive reaction is secured. Caution is necessary to prevent provoking reactions in very sensitive patients. In cases of marked allergy, local reactions may be excited. Generalized phenomena can be instituted, such as various skin dermatoses, fever, lymphadenopathy, asthma or even urticaria. The local skin test is either immediate or delayed (tuberculin-type). A positive test is not diagnostic unless other findings support a mycotic infection. A negative test in an individual of proven fungous disease shows poor or absent immunity. This calls for intensive treatment. A negative test may be due to lack of time, in a case of recent infection, to develop allergy.

The therapeutic value of fungous extracts is controversial.[23] Some authorities feel that their greatest usefulness is in the deep forms of mycotic infection and of generalized dermatoses, while their value is less in the superficial and eczemoid varieties, for there is generally no antibody formation in the latter types. However, I feel that with local application of whale oil and intensive therapy with trichophytin, I can get results in these resistant cases.

Treatment, utilizing trichophytin extracts to produce antibodies, is based upon Hansel's small dose, intradermal injection method. The dilution which first produces a local reaction is used. In a case of 1:100,000 dilution, .02 c.c. can be given intradermally, and small increments such as .02 c.c. may be given every other day. Later the next stronger dilution can be used. If a reaction occurs, as in other types of desensitization, we drop back to previous dosages. Sometimes when good results follow, I repeat the same dosage and omit increases. In a series of forty-six cases that were resistant to whale oil therapy alone, twenty-two were clinically cured by the use of whale oil plus trichophytin. In these cases we were either unable to reach the fungus by direct application of the oil or else there was poor skin antibody production. By stimulation of the skin, using trichophytin antigen, clinical cures were elicited.

With the combined treatment of whale oil and trichophytin (Hollister-Stier extract), cases unsuccessfully treated by whale oil alone are narrowed. It should be mentioned that most of these cases showed some improvement with the whale oil; however, the degree of response was not entirely satisfactory, and they did not go on to a clinical cure until tricho-

phytin was given. A two-month trial period of whale oil alone is used. If progress is steady, even though slow, we continue to go along with just the oil. However, if the case response is poor or static, we consider it a failure and give trichophytin too. The combined therapy is also given a two-month trial period. The same criteria are used to judge the efficacy of this treatment as were set up for the oil alone.

Because of my experience with the use of autoserotherapy in other allergic manifestations, I decided to try it in cases resistant to whale oil-trichophytin therapy. The benefits of autohemotherapy or autoserotherapy are based upon the principle that small quantities of the antigen are present in the blood and will stimulate systemic production of specific antibodies. We know that in epidermophytosis, fungi and their metabolites can get into the blood stream. Spread has been shown to be hematogenous. Therefore, I felt that the "proper antigen" would be in the blood stream. I decided to try this treatment.

Ten or twenty cubic centimeters of whole blood are drawn and the serum extracted. Centrifying may be used to accomplish this. A simple method is to collect the blood in a sterile vial, allow it to clot in the refrigerator, then remove the serum and place in another sterile vial. It should always be kept in the refrigerator.

It is preferable to draw blood when the patient's disease is most active. In this way we can feel certain that the "proper antigen" should be present in the blood stream in adequate amount for antibody stimulation.

Injections are started with 0.1 c.c. doses and increased to 0.2 c.c., all being given intradermally every other day. Four injections are given in the same skin site, then a new site is chosen for the next four and so on. If case response is slow, double sites are injected simultaneously.

Twenty-four cases that did not respond to the combined whale oil—trichophytin—were treated by the combined whale oil—autoserum treatment. At this point it might be asked why we continue to use the oil when cases were not clinically cured by its administration. As shown previously, when trichophytin was used, we did get, in most cases, evidence of fungistatic activity. There was some clearing of lesions and clinical improvement, but we did not get clinical cures. Therefore we felt that we would continue to use the oil along with the trichophytin, and again now with the autoserum, because we did have some results which we wished to hold. The idea was to prevent losing any of our fungistatic gains until fungicidal antibodies could be produced in sufficient amounts to eradicate the mycotic foci. In a very few cases where the whale oil seemed to have no effect, we discontinued using it. Eighteen patients responded of the twenty-four treated by the combined whale oil—autoserum treatment.

Results using the above method are superior to the whale oil—trichophytin treatment. Eighteen cases that did not respond to the latter therapy cleared with the autoserum. Of the six that did not show results, two were not affected by whale oil alone either. The failures noted by the auto-

[illegible] were given an- [illegible] the hospital while on treatment [illegible] In twenty-six patients

NASAL PYRIBENZAMINE FOR RELIEF OF HAY FEVER

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THE value of Pyribenzamine and similar drugs in the treatment of hay fever has been fully established clinically. These preparations, however, present undesirable side effects in a substantial proportion of cases, manifested by dizziness, disorientation, nausea, vomiting, headaches, dryness of the mouth, and mental confusion. The drowsiness interferes with routine activity, and the confusion and disorientation has led to a number of accidents of serious nature. It occurred to us that the local nasal use of Pyribenzamine would require smaller amounts of the drug affording relief of hay fever, and at the same time avoid unpleasant and disagreeable side effects.

Preparation of various concentrations of Pyribenzamine from 0.5 per cent to 5 per cent were made in normal saline and used experimentally to determine the most practical strength solution adaptable for this purpose. It was ascertained that the 1 per cent solution was the most effective therapeutically without producing the usual side effects. Concentrations less than 1 per cent often failed to relieve hay fever symptoms sufficiently, whereas solutions stronger than 1 per cent produced objectionable pharyngeal burning. In addition, the 4 per cent and 5 per cent solutions resulted not only in unpleasant burning of the nasopharynx, but were accompanied also by side effects as seen with oral administration of the drug. A 1 per cent solution contains 0.65 mg. per minim of the drug.

The 1 per cent solution in doses of two or three drops in the nose was, therefore, decided upon and used in sixty-two cases of ragweed hay fever. Of these, twenty-three had also used Pyribenzamine orally during the 1946 and 1947 ragweed pollen seasons. The twenty-three cases using both forms of the drug alternated the use of nasal and oral medication on different days, and the same days, to evaluate the effects. There were two cases which were not relieved by either the oral or nasal medication. The remainder, of which there were twenty-one, preferred the nasal use of Pyribenzamine for the following reasons:

1. Speed of action—four to ten minutes.
2. Duration of relief—four to thirty-six hours.
3. Degree of relief more complete (approaching 100 per cent).
4. Side effects—none, except slight nasal pharyngeal burning noted with any nose medication, and relieved by drinking cold water.

The thirty-three cases treated with pollen injections plus nasal medication could not offer a comparison with the oral route, but obtained

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relief comparable to the group already described. All but six of the entire group of sixty-two cases were treated hypodermically with pollen preparations. The six not receiving pollen, and representing a small group, seemed to be as effectively relieved as the pollen-treated group. Two cases receiving pollen and nasal therapy were relieved of hay fever, but noted slight asthma a few minutes following nasal application of Pyribenzamine.

Of particular interest is the group complicated by asthma during and following the pollen season of 1946. This comprised eleven patients treated also in the 1947 ragweed season, during which three had asthma.

SUMMARY

Pyribenzamine, in a 1 per cent solution used as nasal drops, provides effective relief of hay fever without objectionable side effects, which, at times, have been disastrous. Further, its action used in this manner is more rapid and offers more complete relief of symptoms than does the oral preparation.

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SYNTHETIC ANTIHISTAMINIC DRUGS

(Continued from Page 90)

parison was made against one lethal dose. The relative order of efficacy was the same by both methods.

3. Results in two of three series of antianaphylactic experiments in guinea pigs, in which a drug with a higher antihistamine index was compared with one of lower activity, followed the pattern shown in the histamine studies.

4. Variations in the ability of these drugs to reduce histamine wheals in the human skin were comparable to differences observed in guinea pig experiments.

5. Clinical differences between the six drugs tend to parallel experimental differences, but not necessarily in the same proportion.

REFERENCES

1. Feinberg, S. M.: Conference on antihistamine agents in allergy. New York Acad. Sc. (Oct. 1) 1947.
2. Friedlaender, A. S., and Friedlaender, S.: Pyribenzamine in hay fever and other allergic disorders. J. Lab. & Clin. Med., 31:1350, 1946.
3. Friedlander, S., and Feinberg, S. M.: Histamine antagonists. III. The effect of oral and local use of B-dimethylaminoethyl benzhydryl ether HCl on the wheaing due to histamine, antigen-antibody reactions, and other wheaing mechanisms. Therapeutic results in allergic manifestations. J. Allergy, 17:129, 1946.
4. Friedlaender, S.; Feinberg, S. M., and Feinberg, A. R.: Histamine antagonists. V. Comparison of Benadryl and Pyribenzamine in histamine and anaphylactic shock. Proc. Soc. Exper. Biol. & Med., 62:65, 1946.
5. Friedlaender, S.; Feinberg, S. M., and Feinberg, A. R.: Histamine antagonists. VI. Comparative antihistamine activity of some ethylenediamine drugs in the guinea pig. J. Lab. & Clin. Med., 32:47, 1947.
6. Friedlaender, S., and Friedlaender, A. S.: The effect of antihistamine drugs in various wheaing phenomena. (To be published.)

PERIARTERITIS NODOSA

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As medical investigation progresses, it is becoming apparent that an imposing list of symptom complexes *may* be "allergic diseases." Frequently, undiagnosed disease has simply been termed an "allergic condition," and too often the reasons for claiming a given disease as one due to allergic causes have been frank speculation. Such diseases as rheumatic fever, acute glomerulonephritis, and periarteritis nodosa have been classified by certain authors as allergic in nature.

Some classification of the term "allergy" as applied to these diseases should be attempted. Basically, the term "allergy" can mean only a reaction of antigen and antibody. A classic example is the Arthus phenomenon. Subcutaneous injections of a foreign serum into the test animal at frequent intervals produces a state of sensitization. Subsequent intradermal injection of the antigen in the sensitized animal causes, first, marked inflammation at the site of injection, followed by perivascular infiltration, fibronoid degeneration and finally, necrosis.

It is the purpose of this paper to examine the clinical and experimental evidence in claiming periarteritis nodosa as a disease due to allergy. Kussmal and Maier first described the disease in 1866 as an inflammation of the smaller arteries. In the intervening years, some 400 cases have been reported, most of which were not diagnosed antemortem. Various theories were advanced to establish the causative agent for the unusual disease, including infections, syphilis and so-called toxic reactions. It was not until 1925 that Gruber postulated that periarteritis nodosa might be due to antigen antibody reaction. Following this publication, Vaubel in 1932 and Masugi and Sato in 1934 reported their results of vascular damage in rabbits which had been given large doses of horse serum. These authors were attempting to determine the etiology of rheumatic fever and glomerulonephritis, but their results showed primarily extensive vascular damage resembling that found in periarteritis nodosa. Rich, in 1942, reported a series of four cases which had come to autopsy following serum sickness, presumably due to a hypersensitivity to sulfonamides. All exhibited lesions resembling periarteritis nodosa; and with this incentive, studies were carried out on rabbits sensitized to horse serum. The animals were given purified serum, 10 c.c. kg., and within five days hypersensitivity could be demonstrated by the intradermal injection of 0.1 c.c. of the serum. The rabbits were sacrificed after about thirty days, and all stages of periarteritis nodosa could be demonstrated in the vessels of the heart, lung, testes and liver. Rich concluded that periarteritis nodosa is a manifestation of the anaphylactic type of hypersensitivity, that various types of sensitizing antigens are responsible for periarteritis nodosa in man, and that there is danger in continued administration of sulfonamides or foreign serum after

a hypersensitive reaction has occurred. This is the most complete work which has been published in the experimental production of the disease and would seem to establish a definite etiology. However, in 1946, Logue and Mullins reported a series of eleven cases in whom they state the causative agent is unknown. None of the patients had received sulfonamides or other known sensitizing agents, with one exception. This was a thirty-one-year-old male who had been given yellow fever vaccine in March, 1942, and in October of the same year developed symptoms.

If periarteritis nodosa is to be classified as an allergic disease, certain criteria must be met in its pathology. Anaphylactoid hypersensitivity produces the following tissue changes:

1. Perivascular infiltration with a fair percentage of eosinophiles and polymorphonuclear cells.
2. Edema of the vascular wall.
3. Fibrinoid necrosis (most important).
4. Blood eosinophilia (variable).

We are fortunate in having some slides from the Department of Medicine of Emory University School of Medicine which demonstrate the various stages of these processes and illustrate how closely the pattern follows that of the hypersensitive state.

The acute stage of periarteritis nodosa manifests itself pathologically by an acute inflammatory infiltration which may reach both intima, media, and adventitia. Often there is more involvement on one side of the vessel wall than the other; this phenomenon of "segmental involvement" is characteristic of periarteritis nodosa. As the process continues, actual infarction of the vessel wall may take place, and, in turn, this may lead to aneurysmal formation. Thrombosis and occlusion of the vessel lumen ensues as a result of the healing process by fibroblastic proliferation.

The symptomatology may be briefly considered. Obviously, the stage of the disease and the vessels involved are responsible for any manifest symptoms, and since the vascular system in almost any part of the body may be affected, they may be protean. Bohrod has summarized the situation adequately as follows:

1. Symptoms of the inflammatory state—intermittent fever, leukocytosis, increased sedimentation rate, cachexia.
2. Symptoms at site of involvement.
3. Symptoms of nonvascular accompaniments—nephritis, liver necrosis, granulomas.
4. Symptoms related to complications, such as infarcation, rupture of aneurysm, et cetera.

Certain portions of the vascular system are more frequently involved than others. Primarily, the disease affects the medium-sized vessels,

rarely the large arteries or arterioles. The heart, kidneys, gall bladder and testes are most often attacked, with symptoms pointing to these organs as a principal complaint.

The diagnosis is difficult and has been made only occasionally before death. Pulsating nodules are diagnostic but occur in a fairly small number of cases. They may be found in the skin and retinal arteries when present. Biopsies are significant only if positive. Eosinophilia may occur in about a third of the cases. It is not a constant finding and seems to be related to the acute exacerbations of the disease. It is interesting that in Rackemann's series of 229 reviewed cases, nineteen had asthma. These asthmatic patients had a very high blood eosinophilia, ranging from 35 per cent to 85 per cent. It was stressed that any patient with asthma, high eosinophilia and pain and numbness of the extremities should be suspected of having periarteritis nodosa.

Periarteritis nodosa usually has a gradual onset with a duration of months or even years. Remission and relapses are common, and probably 5 to 10 per cent recover completely. With better diagnoses, this rate of recovery will increase.

The recent literature has emphasized the occurrence of periarteritis nodosa lesions following serum sickness. While the symptoms of serum sickness result from damage to the capillaries and lymph channels, the pathological reaction appears to be identical with that found in periarteritis nodosa. The nature of the structures involved makes the reactions in serum sickness a reversible one, with ultimate recovery the rule and the residual damage to the affected areas not too serious. This same process, involving the medium-sized arteries, often is irreversible, with permanent damage to the tissues supplied by the affected vessels. It thus appears that the two diseases, periarteritis nodosa and serum sickness, are identical processes affecting different areas of the vascular system. Serum sickness is recognized as a true antigen-antibody reaction, and the analogy drawn would necessarily place periarteritis nodosa in the same category.

The number of cases of periarteritis nodosa reported has increased steadily during the last ten years. This could be due to more careful and accurate diagnosis, or there might be some connection with the tremendous strides made in chemotherapy during the past decade. The antigenicity of the sulfonamides has been proved. The mechanism involved is one of hapten formation from sulfonamide plus body protein. The sensitizing properties of penicillin are quite well known, and the literature contains case reports involving penicillin in serum sickness. As far as we know, there have been no reported cases of periarteritis nodosa following the administration of penicillin, but our contention is that any substance which can produce an allergic reaction is a potential cause of periarteritis nodosa in the susceptible patient.

These assumptions may have a particular significance for this group.

(Continued on Page 112)

SEPARATION BY MEANS OF AMMONIUM SALTS OF THE ANTI-BODY-ANTIGEN REACTION FROM THE RESPONSE OF THE SMOOTH MUSCLE

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BY serendipity we found that ammonium sulfate inhibits the effect of histamine upon the isolated gut of the guinea pig and also the reaction of the ileum of sensitized pigs to the homologous antigen. Though for extraneous reasons the investigation remains not as complete as may be desired, the data appear to be interesting enough to merit communication.

MATERIALS AND METHODS

For tests with histamine and other drugs, the isolated ileums of guinea pigs were used.

For tests with anaphylactically sensitized guinea pigs, animals were either injected about forty-eight hours before test with 2 to 3 ml. of the corresponding rabbit immune sera, or guinea pigs were used which had been actively sensitized about three weeks before the test by small subcutaneous injections of the respective antigen.

As antigens, either whole unpreserved normal horse serum or a solution of granulated commercial (crude) pepsin was employed. For reasons which will presently become clear, the use of material containing more than one antigen was advantageous to our purpose. Horse serum harbors a number of protein antigens. The crude pepsin contains at least two antigens, namely, one corresponding in its specificity to antigen contained in pig serum, and another one of unknown nature, of which it can only be said that it is not antigenically related to material contained in the serum or in extracts from muscle or dander of hogs; as tests with a crystalline pepsin* of porcine origin have shown, it is also not identical with the enzyme itself.

Tests were made in a small Dale apparatus of typical construction. The bath in which strips of ileum of approximately 2 cm. in length were suspended had a capacity of 80 ml. From this, concentrations can be easily calculated from the data given in the following paragraphs. The bathing fluid was Ringer-Locke solution, and the same medium was used for making dilutions of the agents employed in the test.

RESULTS

The following ammonium salts were employed: the chloride, sulfate, and lactate. The corresponding sodium salts did not have similar effects. Therefore it appears that the effective part of the salts is the ammonium ion. Relatively high concentrations are needed: they are in the order of

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Present address of Dr. Weil: Bronx Hospital, New York St., N. Y.
* The crystalline pepsin was obtained from Dr. Klarmann of Lehn and Fink Products Corporation, Bloomfield, New Jersey.

1/40 to 1/10 molarity. The inhibition can be removed by washing, as can be seen from Figure 1. There is some difference in the behavior of the different ammonium salts, in that the time needed for removal by washing varies. Ammonium sulfate or chloride can be removed by a single

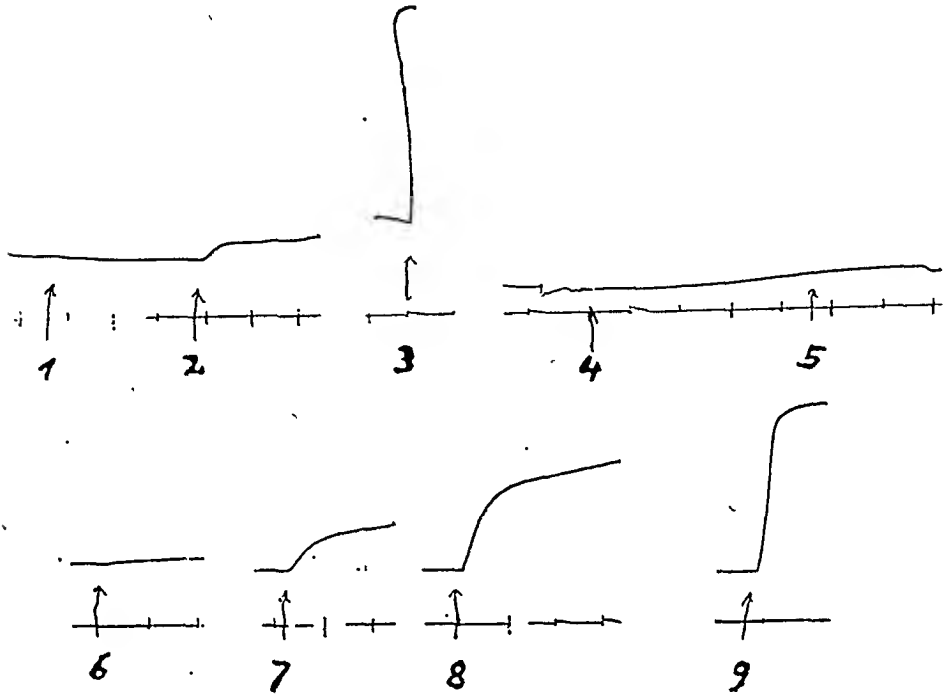

Fig. 1. Illustration of inhibition of histamine by ammonium salts. Each interruption of the tracing signifies three washings, which take one to two minutes of time.

Arrow (1) 8.0 M/1 ammonium sulfate. (2) 1.0 × 10^{-5} histamine diphosphate. (3) histamine as in (2). (4) 8.0 M/1 ammonium lactate. (5) through (9) histamine as in (2).

It will be seen that ammonium sulfate is removed by one set of washings, whereas ammonium lactate is only gradually washed out.

sequence of three washings, whereas more repeated washings, or an interval of about five minutes between the second and third washings, are needed in order to make the effect of ammonium lactate disappear.

The inhibition is relatively independent of the dosage of histamine. The same amounts of ammonium salt inhibits an approximately 50 per cent maximal contraction as obtained by concentrations of histamine of 1.0 × 10^{-9} and concentrations 1,000 times higher.

Acetylcholine is also antagonized, though slightly higher concentrations of ammonium salt are needed, and, correspondingly, the inhibition is more easily removed by washing.

The contraction of the isolated gut of the sensitized guinea pig on addition of the homologous antigen to the bath is inhibited by ammonium salts in the same concentration as are effective for histamine and acetyl-

choline. This inhibition does not affect the combination of antigen and antibody, as could be shown by the following experiments:

In preliminary tests the dose of antigen is determined which completely desensitizes a strip of ileum, as demonstrable by the lack of reaction to a

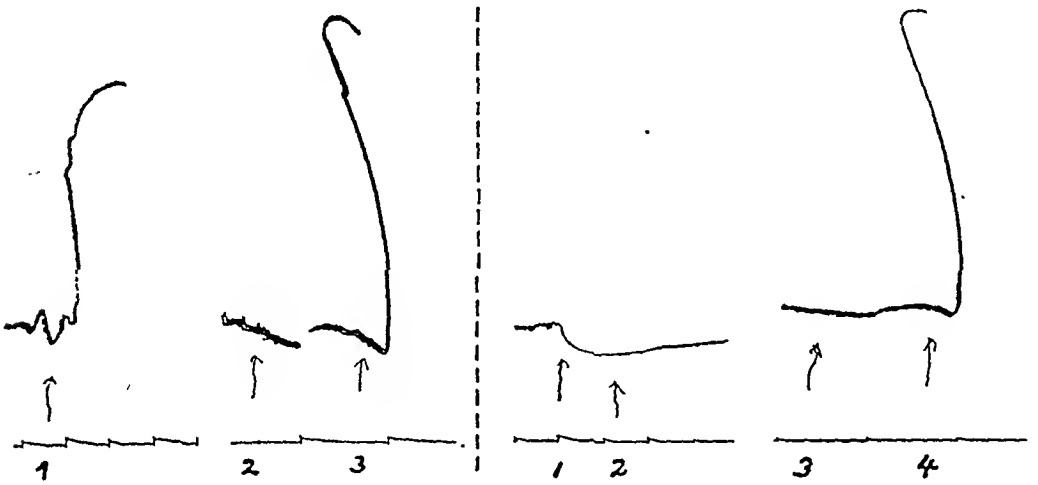

Fig. 2. *Left tracing.*—Arrow (1) 0.1 ml hog serum. Then, after three washings: (2) 0.1 ml hog serum. (3) 0.01 g crude pepsin in Locke's solution.
Right tracing.—Arrow (1) 8.0 M/1 ammonium sulfate. (2) 0.1 ml hog serum. Then, after three washings: (3) 0.1 ml hog serum. (4) 0.01 g crude pepsin in Locke's solution.

second dose of antigen. If a similar experiment is made after addition of ammonium salt to the bath, the first dose of antigen does not cause contraction, but desensitization is nevertheless obtained. When the preparation is washed to the point where the ammonium effect has vanished, and a second dose of antigen is introduced, no contraction can be elicited, though the contractibility of the preparations is fully restored, as can be seen from the subsequent addition of histamine or acetylcholine to the bath, which cause prompt contraction.

The evidence becomes still more convincing in the second type of experiment. In the strip of a guinea pig sensitized to a complex antigen, desensitization is obtained only against the first antigen introduced. For instance, the completely desensitizing dose of hog serum for the ileum of a guinea pig sensitized to crude pepsin was determined; after washing, a second dose of hog serum does not cause contraction, but the strip remains reactive to the additional antigen contained in the pepsin preparation, as can be shown by its reactivity to dissolved pepsin. The same experiment is then repeated, except that ammonium salt is added to the bath about a half a minute before the hog serum is added for the first time. No contraction is seen. The preparation is suitably washed and hog serum is introduced for the second time. Again no contraction is observed. That this is due to desensitization and not to a persistent effect of the ammonium salt becomes clear when crude pepsin is added.

Maximal contraction promptly occurs, thus demonstrating that anaphylactic reactibility *per se* has not been disturbed by the contact with ammonium salt. An experiment of this kind is reproduced in Figure 2.

A similar sequence of events can be shown with guinea pigs sensitized to whole horse serum. Desensitization to one of the antigens, for instance, by employing a water-insoluble globulin fraction,** can be obtained regardless of whether or not desensitization is inhibited by ammonium salt; and the restoration of anaphylactic reactivity and partial desensitization can be demonstrated, after suitable washing, by first adding again the globulin (no contraction) and then whole serum (prompt contraction).

Ammonium salts *in vivo* are rather toxic, and concentrations effective for suppressing histamine and anaphylactic reactions are on the borderline of the lethal concentration. Such concentrations also cause strong local reactions when introduced subcutaneously and intraperitoneally. Thus, this method cannot be adapted to experimentation in the living animal.

DISCUSSION

Histaminic and anaphylactic reactions can be suppressed by several agents. Arginin, histidin and cystein have been found to antagonize the effect of histamine,[2,5] and so do substances such as urethane.[3] More recently, a new group of antihistaminic drugs has been discovered.[4,8] Ammonium salts may be added to this list. It appears, however, that the various agents differ greatly in their mode of action. This becomes obvious if the concentrations needed for the suppression of histamine reactions are considered. One molecule of some of the new antihistaminic drugs will antagonize the effect of up to 100 molecules of histamine on the isolated guinea pig ileum[6,7,9]; with others, the ratio is about one to one[1]; about forty molecules of arginin are needed in order to suppress the effect of one molecule of histamine; and the ratios of urethane and of ammonium salts are still higher, as evidenced from previous data[3] and in this report. Also, ammonium salts antagonize acetylcholine, whereas only some of the new antihistaminics of the ethylenediamine group have this ability.[4,6,10]

At the present preliminary state of the investigation of ammonium salts, it would be futile to speculate upon the mechanism by which they act. Ammonium salts appear to be promising tools for the investigation of the mechanism of anaphylactic reaction. Like urethane,[3] they do not suppress the combination of antigen and antibody, as evidenced by the observation that desensitization can be obtained without contraction of the smooth muscle fibers. The possibility of removing the agent by washing is likely to be a circumstance favorable for the urgently needed further

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investigation of the problem of why the combination of antibody and antigen should have such powerful pathological effects.

SUMMARY

Ammonium salts in concentrations in the order of 1/10 molarity suppress the contraction of the isolated ileum of the guinea pig as caused by histamine, acetylcholine, and the anaphylactic contraction of the gut of the sensitized guinea pig. The effect can be removed by washing. Ammonium salts do not affect the combining of antibody and antigen, as evidenced by the fact that desensitization can be obtained in their presence.

REFERENCES

1. Dreyer, N. B., and Harwood, D.: Proc. Soc. Exper. Biol. & Med., 66:515, 1948.
2. Edlbacher, S.; Jucker, P., and Baur, H.: Ztschr. physiol. Chem., 247:63, 1937.
3. Farmer, L.: J. Immunol., 33:9, 1937.
4. Feinberg, S. M.: Am. J. Med., 3:560, 1947.
5. Landau, S. W., and Gay, L. N.: Bull. Johns Hopkins Hosp., 74:55, 1944.
6. Litchfield, J. T., Jr.; Adams, M. R.; Goddard, L.; Jaeger, M. S., and Alonso, L.: Bull. Johns Hopkins Hosp., 81:55, 1947.
7. Mayer, R. L.; Huttrer, C. P., and Scholz, C. R.: Science, 102:93, 1945.
8. Rose, B.: Am. J. Med., 3:545, 1947.
9. Winter, C. A.: Federation Proc., 6:228, 1947.
10. Yonkman, F. F.; Oppenheimer, E.; Rennick, B., and Pellet, E.: J. Pharmacol. & Exper. Therap., 89:31, 1947.

PERIARTERITIS NODOSA

(Continued from Page 107)

Of the recorded cases, over 20 per cent have had a history of some allergic manifestation. The case of evoking the antigen-antibody response in these people should encourage caution in the administration of substances which have such high potential antigenic properties.

SUMMARY

1. There are many diseases of indefinite etiology which present many suggestive factors indicating that the basic allergic reaction is involved.

2. The best proof, on clinical and experimental grounds, seems to be in the case of periarteritis nodosa.

REFERENCES

1. Clark and Kaplin: Arch. Path., 34:458, 1937.
2. Logue and Mullins: Ann. Int. Med., 24:11-26, 1946.
3. Rackemann and Greene: Tr. A. Am. Physicians, 54:112, 1939.
4. Rich: Bull. Johns Hopkins Hosp., 71:123, 1942.
5. Rich and Gregory: Bull. Johns Hopkins Hosp., 72:65-68, 1943.

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EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHOSPASM

III. Anticholinergic Agents

JOHN F. BEAKEY, M.D., ELLIOTT BRESNICK, M.D., LEON LEVINSON, M.D., and MAURICE S. SEGAL, M.D., F.A.C.A.
Boston, Massachusetts

IT HAS been the opinion of many investigators that bronchial asthma may represent an imbalance of the autonomic nervous system. In 1909, Eppinger and Hess,[3] in developing their theory of vagotonia, included bronchial asthma as an example of "pathological vagotonia." This concept persists and has given rise to considerable conjecture in various quarters. We have previously discussed the historical aspects of this theory.[6,9]

If bronchial asthma is due to an overactivity of the cholinergic apparatus, then it should respond most satisfactorily to treatment with drugs which block the action of these nerves. In this report we will describe the results obtained by testing the efficacy of various anticholinergic agents in protecting against dyspnea and bronchospasm artificially induced in human subjects with histamine and acetyl-beta-methylcholine administered intravenously and as an aerosol.

The classic agents which inhibit the action of cholinergic nerves of the postganglionic type are alkaloids of the belladonna group. There are various synthetic substances of the ergot family and other laboratory curiosities which exhibit similar parasympatholytic activity, but in practice the belladonna alkaloids furnish the optimum drugs of this class. This group of alkaloids consists in the main of two, hyoscine and hyoscyamine. Both of these alkaloids are salts of a complex organic acid, tropic acid, with a complex base, tropine in the case of hyoscyamine, and scopine in the case of hyoscine. The two bases differ only in the presence of an oxygen bridge between two adjacent cargon atoms.[5]

Each of the alkaloids exists in nature in dextro-rotatory and levo-rotatory forms. In each case it is predominantly the levo-rotatory form that is pharmacologically active, the dextro-rotatory isomers being largely or totally inert. Atropine, as clinically available, consists of a racemic mixture of levo- and dextro-hyoscyamine. Most of its action on the autonomic nervous system is due to the contained levo-hyoscyamine. Scopolamine consists almost completely of levo-hyoscine. There is a drug, atroscine, consisting of racemic hyoscine, which is the proper analogue for atropine; it is not used clinically. There is also a large family of synthetic derivatives or imitations of these alkaloids containing various bases and acids in similar linkage which mimic the action of the belladonna group. We have limited this study to the use of the two common clinically available alkaloids, atropine (racemic hyoscyamine) and scopolamine (levo-hyoscine).* In order to compare the effects of hyoscine and hyoscyamine directly we have also made use of a preparation of mixed belladonna alkaloids which has been assayed in terms of levo-hyoscyamine only (Bellafoline-Sandoz).**

TECHNIQUE

The historical development and technique of assay in man of these and other agents, new or old, employed in the management of bronchial asthma, have pre-

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*Kindly supplied through the courtesy of Hoffman-LaRoche, Inc., Nutley, New Jersey.
**Kindly supplied through the courtesy of Sandoz Chemical Works, Inc., New York, N. Y.

viously been reported.[6,9] In brief, protection studies consist of observations of the decrease in vital capacity produced by repeated administration of a suitable bronchospastic agent (in this report, histamine† or acetyl-beta-methycholine‡) before

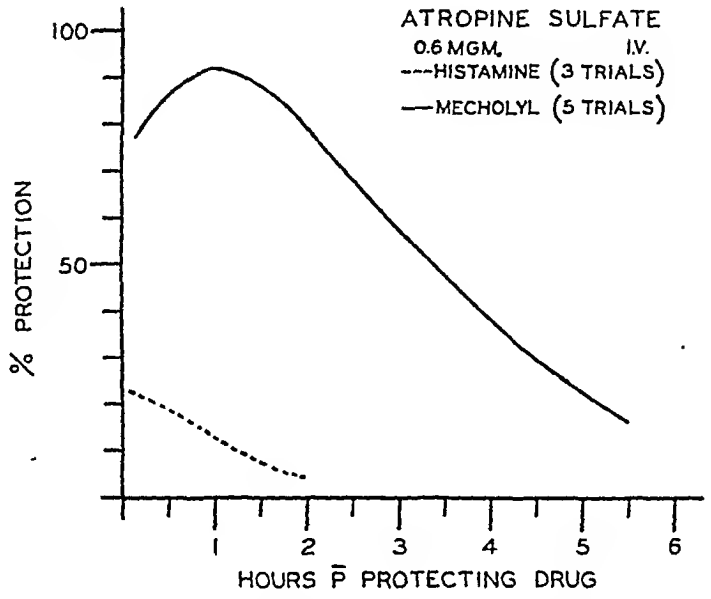

Fig. 1. The protecting capacity of atropine sulfate, 0.6 mg. given intravenously, against the bronchospastic effects of intravenous histamine and Mecholyl.

and after administration of the therapeutic agent in question. The degree of protection afforded by the therapeutic agent is described in terms of the following equation:

$$P = \frac{C - E}{C} \times 100,$$

where P is the degree of protection in per cent, C the control drop in vital capacity occurring after administration of the bronchospastic substance before the protecting drug is given, and E the drop similarly produced at any time after the protecting agent has been administered. The many points which make up any one curve are derived according to this protection equation and represent the average of several trials in different subjects.

RESULTS

The protecting effect of atropine sulfate, the most commonly used anticholinergic drug in a dose of 0.6 mg. given intravenously, is depicted in Figure 1. Atropine, in the dose administered, is capable of protecting a susceptible individual against the effects of subsequent doses of intravenous Mecholyl to an almost complete degree (80 per cent or higher) for a period of approximately two hours. Significant or 40 per cent protection continues for four hours after atropine has been given. The bronchospastic effects of intravenous histamine are, however, little reduced by atropine.

Bellafoline, a mixture of total levo-rotatory belladonna alkaloids, has been investigated in considerably more detail. After intravenous injection of 0.5 mg. of

†Kindly supplied through the courtesy of Abbott Laboratories, North Chicago, Illinois.
‡Kindly supplied through the courtesy of Merck and Company, Rahway, New Jersey (Mecholyl Chloride), and hereinafter referred to simply as Mecholyl.

Bellafoline, the bronchospastic effects of intravenous administration of Mecholyl are inhibited to an even greater degree than following the administration of a similar dose of atropine (Fig. 2). Such superiority of the levo-rotatory preparation over

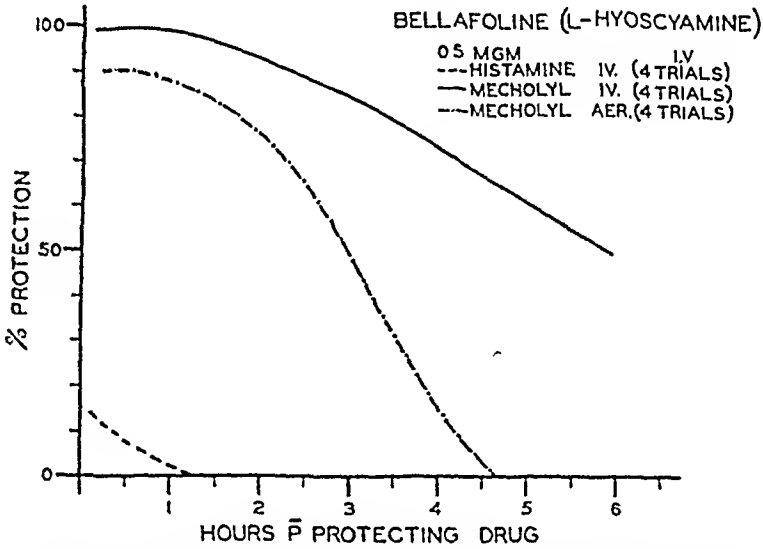

Fig. 2. The protecting capacity of Bellafoline, 0.5 mg., given intravenously, against the bronchospastic effects of intravenous histamine and of intravenous and aerosol Mecholyl.

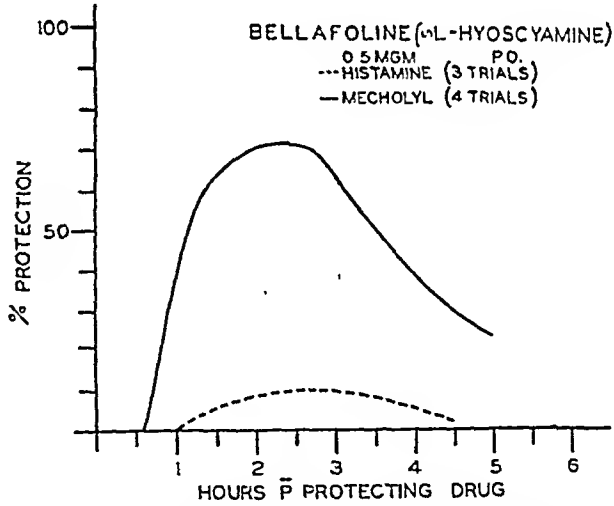

Fig. 3. The protecting capacity of Bellafoline, 0.5 mg. given by mouth against the bronchospastic effects of intravenous histamine and Mecholyl.

the racemic mixture is, of course, predictable. Essentially complete protection persists for a period of three hours, and significant, or 40 per cent, protection persists for a period of at least six hours, the maximum duration of these experiments. The bronchospastic effects of intravenous histamine are not affected by Bellafoline, as was similarly observed with atropine. These results, derived from many

experiments, differ from those reported by Curry,[1] which were based on a single study.

The effectiveness of intravenous Bellafoline against intravenous Mecholyl led us

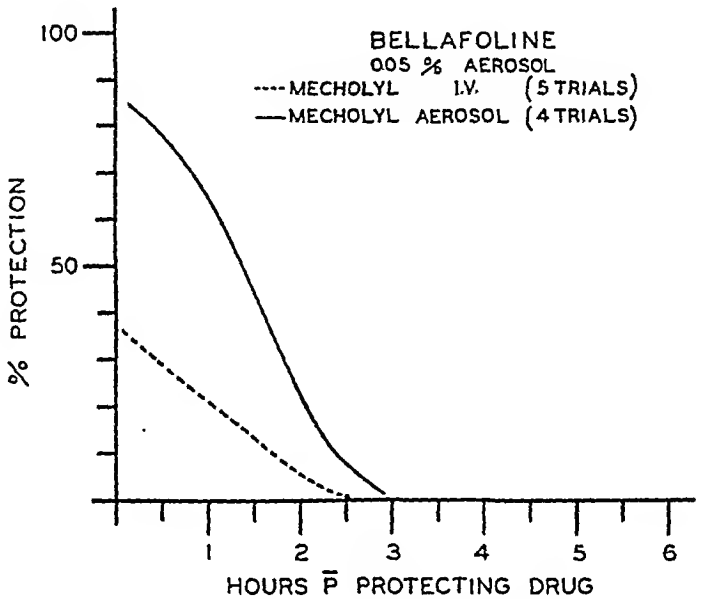

Fig. 4. The protecting capacity of Bellafoline, 0.05 per cent given as an aerosol, against the bronchospastic effects of intravenous and aerosol Mecholyl. The dose of Bellafoline was six deep inhalations of the mist produced from this solution by the Vaponefrin nebulizer.

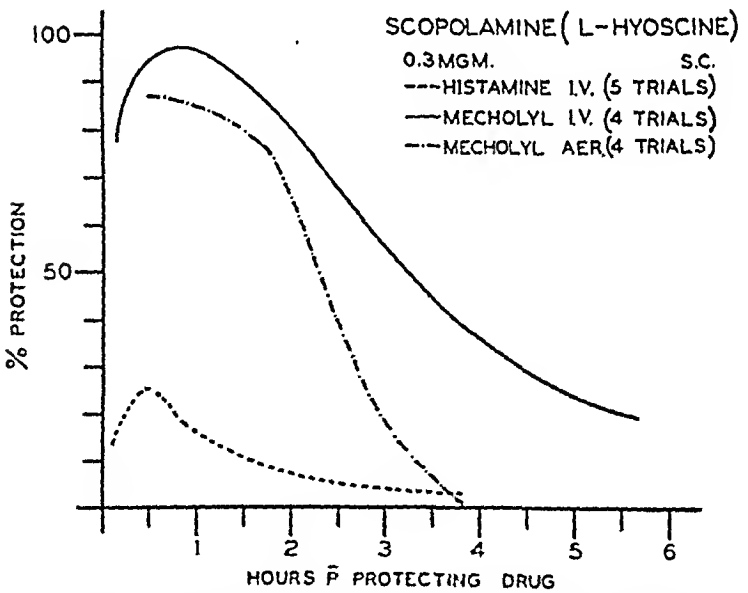

Fig. 5. The protecting capacity of scopolamine, 0.3 mg. given subcutaneously, against the bronchospastic effects of intravenous histamine and of intravenous and aerosol Mecholyl.

to investigate its protective capacity after oral and aerosol administration. The results of these studies are shown in Figures 3 and 4. Orally administered Bellafoline (0.5 mg.), the same dose as used by vein, is less active, but it still protects against the effects of intravenous Mecholyl for a period of three hours, after a

one-hour latent period presumably denoting the delay incident to absorption. When administered as an aerosol, Bellafoline has little or no protecting action against intravenous Mecholyl. However, when the conditions of the experiment are

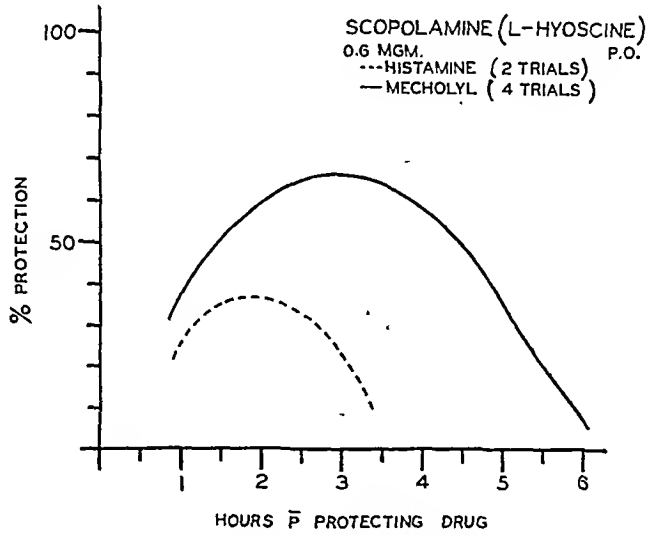

Fig. 6. The protecting effect of scopolamine, 0.6 mg. given by mouth, against the bronchospastic effects of intravenous histamine and Mecholyl.

altered by administering the bronchospastic agent as an aerosol as well, it is found that aerosol Bellafoline will protect against aerosol Mecholyl for almost two hours. Intravenous Bellafoline protects against aerosol Mecholyl for three and one-half hours (Fig. 2). The disparity in results obtained by the use of the same drugs via different routes will be discussed below.

Scopolamine represents the other major belladonna alkaloid, levo-hyoscine. Results obtained with this preparation are depicted in Figures 5, 6, and 7. An exactly comparable dose of scopolamine could not be employed in these experiments because of its pronounced sedative side reactions. Like the other drugs scopolamine has no significant protecting action against histamine. Its protecting ability against Mecholyl approximates that of atropine (a given amount of scopolamine contains roughly twice as much of the active levo-rotatory alkaloid as does the same amount of atropine). When administered subcutaneously in a dose of 0.3 mg., scopolamine protects against intravenous Mecholyl almost completely for two hours and to a significant degree for a total of three and one-half hours. The protecting ability of subcutaneous scopolamine against aerosol Mecholyl is less marked (Fig. 5). Orally administered scopolamine, in a dose of 0.6 mg., exhibits significant protection against intravenous Mecholyl for more than four and one-half hours, after a latent period of about one hour (Fig. 6). The degree of protection, however, is less than with subcutaneous scopolamine, even though a larger dose was employed. Aerosol scopolamine has a shorter duration of protecting action than the same drug given orally or subcutaneously (Fig. 7). The difference between the effects of aerosol scopolamine upon the bronchospastic effect of Mecholyl given by vein and as an aerosol is not as marked as was the case with Bellafoline and may not be significant.

We have demonstrated that each of the belladonna alkaloids acts as an almost complete inhibitor of the effects of administered Mecholyl for an appreciable period

of time and that they display apparently no significant effect against administered histamine, regardless of the method of administration of either agent.

To be certain that we are dealing with a direct effect of the injected Mecholyl

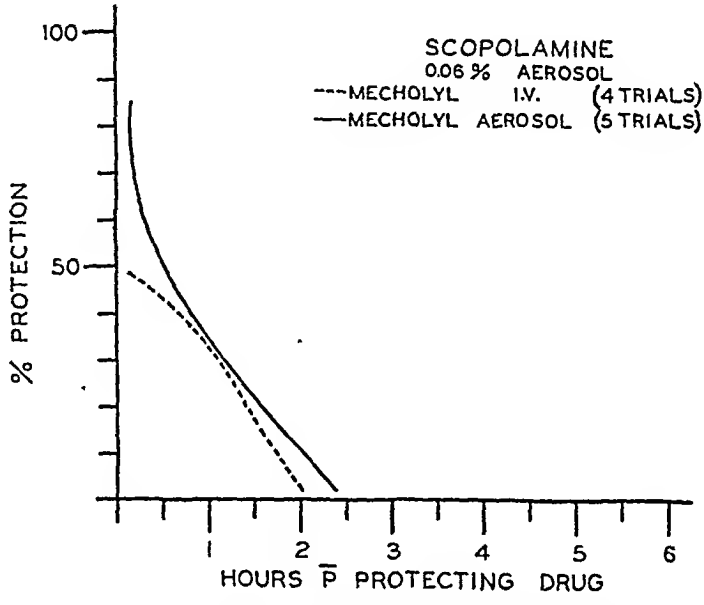

Fig. 7. The protecting capacity of scopolamine, 0.06 per cent solution administered as an aerosol, against the bronchospastic effects of intravenous and aerosol Mecholyl. The dose of scopolamine was six deep inhalations of the mist produced from this solution by the Vaponefrin nebulizer.

and not with some phenomenon due to a secondary reaction of the organism, we have endeavored to demonstrate the potentiating effect of neostigmine, a physostigmine derivative, on bronchospasm induced by Mecholyl (Fig. 8). It is evident that it is easy to produce a marked increase of Mecholyl-induced bronchospasm by previous administration of neostigmine.

In many experiments involving the use of these parasympatholytic alkaloids a striking sedative action has been noted. In some cases the subcutaneous administration of 0.3 mg. of scopolamine has resulted in deep drowsiness or sleep lasting for as long as two to three hours. Similar reactions have been noted with Bellafoline. Sedation was less evident following atropine, which was to be expected.

DISCUSSION AND CONCLUSIONS

Comparison on a weight basis of the various anticholinergic agents employed is obviously unsound, since atropine is a racemic mixture, whereas scopolamine and Bellafoline represent optically and pharmacologically active levo-rotatory alkaloids. With this fact in mind, one may conclude from these experiments that the anticholinergic properties of levo-hyoscine and levo-hyoscyamine are probably identical, within the limits of error of the techniques employed, in annulling the effects upon the bronchial musculature of subsequently administered Mecholyl. This is certainly true with regard to the parenteral and oral routes of administration; the apparent superiority of Bellafoline over scopolamine when these compounds are employed as aerosols is unexplained.

It may be perceived from the data presented that in each case a protecting agent reaching its site of action via the blood stream seems more efficacious in combatting the effects of a bronchospastic agent administered by the same route. A protecting drug given as an aerosol is more potent against bronchospastic aerosols

than against bronchospastic agents given by vein. This finding is difficult to interpret. One may speculate that aerosols reach the motor end-plates of the bronchial musculature by a path differing from that taken by substances reaching the lung via the pulmonary circulation. Perhaps aerosols and blood-borne medications do not exert their action entirely in the same effector area; the protecting agent given by one route "covers" all the effectors which may be reached by a bronchospastic drug later administered by the same route, but leaves "uncovered" some other effectors which still remain sensitive to bronchospastic agents administered via a different route. This concept may have wider applicability to the rationale of treatment of bronchial asthma, particularly in resistant cases, and may indicate the advisability of simultaneous aerosol and intravenous medication. This reasoning is somewhat similar to what we have demonstrated as fact in a study of the pharmacodynamics of pulmonary absorption of penicillin in suppurative diseases of the lung.[4] The same hypothesis may cast some light on the variations in response to therapy of patients with "extrinsic" (inhalant) and "intrinsic" asthma.

Clinically, it is well known and accepted that atropine is not an effective bronchodilator and that it is almost useless in the treatment of bronchial asthma. In addition, its drying action on the mucous membranes of the tracheobronchial tree leads to further inspissation of already semi-solid mucus plugs. This makes coughing and expulsion of mucus plugs an even more difficult task for the asthmatic patient and renders him more liable to recurrent bronchospasm and to obstructive atelectasis. Despite the excellent ability of these medications to combat the effects of injected Mecholyl in the laboratory, atropine, scopolamine, or Bellafoline will serve a very limited role in the therapeutic armamentarium of the pneumatologist in his attempt to counteract the bronchospasm of bronchial asthma. Scopolamine has a stronger action than atropine on the secretory glands and has a far more marked central sedative effect; the latter is highly desirable in many cases. The wet, sweating, hypotensive asthmatic patient who may be exhibiting a systemic picture of parasympathetic stimulation ("pathological vagotonia") is almost completely resistive to ordinary methods of treatment. It is possible that hyoscine, hyoscyamine, or a derivative, may exhibit sufficient sedative as well as bronchosypasmolytic properties in such asthmatic patients that its use might be indicated in spite of its drying action. We hope that the pharmacologist will be able to devise a compound retaining the sedative action and the usual anticholinergic properties of the parent drug, but with less local effect on the bronchial mucosa.

The results of these experiments demonstrate, then, that the alkaloids of the belladonna group are, as could have been predicted, dramatic inhibiting or protecting agents against the deleterious bronchospastic effects of injected Mecholyl and that they have little or probably no effect on the bronchospasm produced by the administration of histamine. Although these results may have little clinical value, they offer some theoretical significance. We are dealing in bronchial asthma with a disease of unknown pathogenesis. It has been suggested that acetylcholine acts in the asthmatic patient upon a sensitive end organ, the bronchial musculature and submucosa, to produce bronchial edema ("the bronchial hive"), bronchial muscular constriction, and thereby bronchospasm resulting in an attack of asthma. We have been able to show conclusively that injected Mecholyl has similar effects but that these effects may be completely inhibited by pretreatment with an alkaloid of the belladonna group. On the other hand, these alkaloids alone are ineffective in the treatment of clinical asthma.

These observations are essentially similar to those of Dale and Gaddum,[2] who studied the contracture which occurs in denervated voluntary muscle when the parasympathetic vasomotor fibers supplying the vessels within the muscle are stimulated. This contracture occurs, beyond doubt, by the diffusion of acetylcholine, liberated in the walls of the blood vessels in response to vasoconstrictor

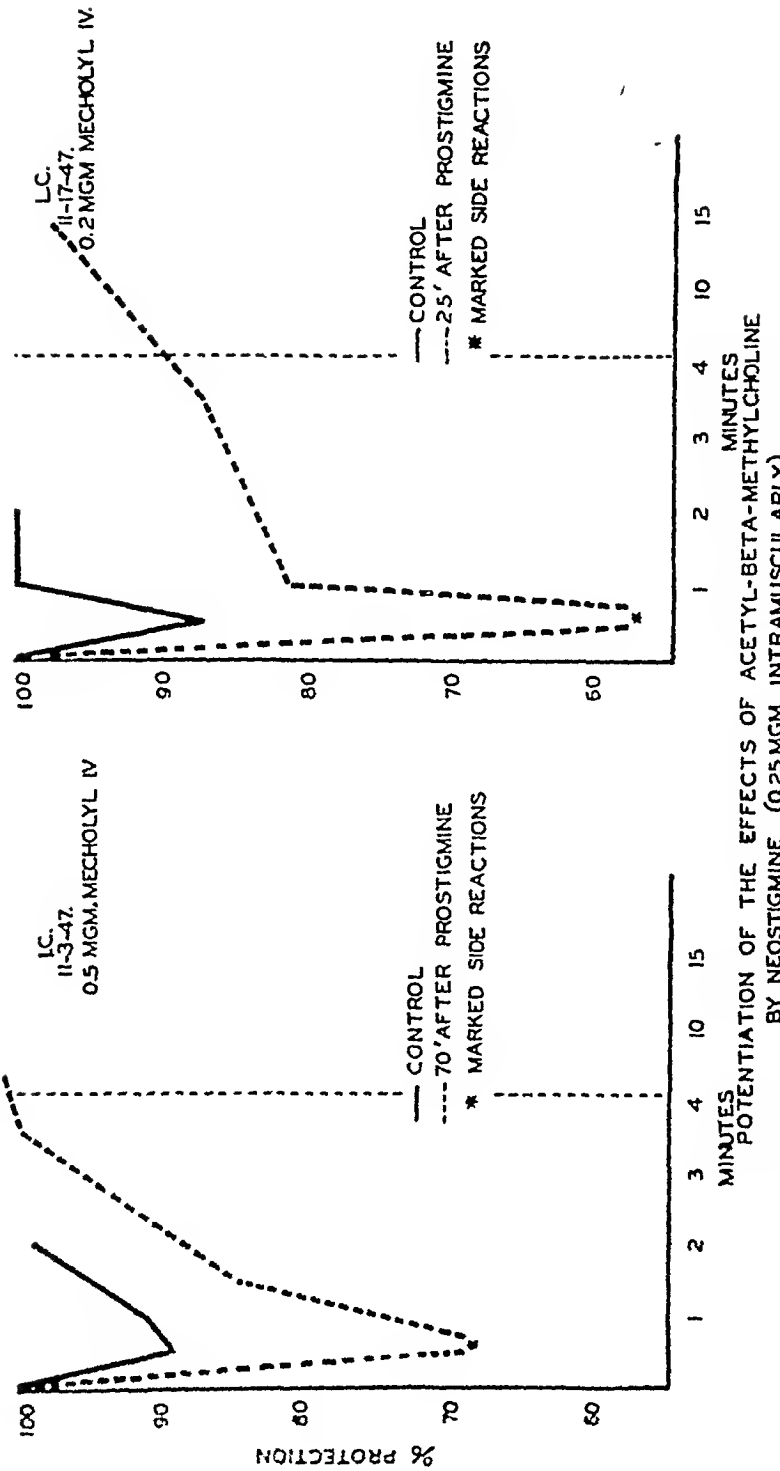

Fig. 8. The potentiating effect of neostigmine, 0.25 given intramuscularly on the bronchospastic effect of Mecholyl.

impulses, into the neighboring muscle tissue. However, the contracture was not prevented by atropine. Dale and Gaddum propose that in this and similar situations the liberation of acetylcholine occurs in an anatomical area so close to the effector tissue that atropine is unable to exert its usual inhibitory effect. Such a mechanism may also be present in the bronchioles. Alternatively, one would be forced to conclude that bronchial asthma is not a phenomenon of parasympathetic-sympathetic imbalance.

If bronchial asthma is not a "vagotonic" phenomenon, what is it? It might be due entirely to histamine and a phenomenon of histamine shock. Further publications in this series will describe the protecting effect of antihistaminic agents and their relationship to bronchial asthma.[10] It is, of course, quite likely that bronchial asthma might be due to the presence in the circulating blood of another chemical mediating substance, the nature of which is purely speculative. Peters and Silverman,[8] studying a soldier with heat allergy, were unable to reduplicate his symptoms by the administration of either histamine or of an acetylcholine derivative alone, but a mixture of the two substances was able to reproduce the wheals of which the patient complained. Such a dual mechanism is also possible in bronchial asthma. A last possibility is that the reaction occurring in bronchial asthma is one localized to the "shock organ" itself.[7] However, the simultaneous occurrence of allergic dermatitides, hives, sneezing, conjuctivitis and asthma after the exposure of a sensitive subject to one allergen leaves this theory insufficient to explain the observed facts.

SUMMARY

1. The results obtained in measuring the protecting ability of atropine, Bellafoline and scopolamine in inhibiting bronchospasm produced by intravenous and aerosol administration of acetyl-beta-methylcholine and intravenous histamine are presented.

2. The possible use of these belladonna alkaloids in clinical asthma, as sedatives and as anticholinergic agents, is discussed from both the favorable and unfavorable pharmacologic aspects.

3. Speculation with regard to the pathogenesis of bronchial asthma, with special emphasis on the role of the parasympathetic nervous system, is presented in the light of these results.

REFERENCES

1. Curry, J. J.: The effect of antihistamine substances and other drugs on histamine bronchoconstriction in asthmatic subjects. J. Clin. Investigation, 25:792, 1946.
2. Dale, H. H., and Gaddum, J. H.: Reactions of denervated voluntary muscle, and their bearing on the mode of action of parasympathetic and related nerves. J. Physiol., 70:109, 1930.
3. Eppinger, H., and Hess, L.: On the pathology of the vegetative nervous system. Ztschr. f. klin. Med., 67:345, and 68:205, 1909.
4. Gaensler, E. A.; Beakey, J. F., and Segal, M. S.: Pharmacodynamics of pulmonary absorption in man, I. Aerosol and intratracheal penicillin. (Submitted for publication.)
5. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York. The Macmillan Company, 1941.
6. Levinson, L.; Beakey, J. F.; Bresnick, E., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm, II. Historical development and methods. (Submitted for publication.)
7. Moll, H. H.: The action of parasympathetic-mimetic drugs in asthma. Quart. J. Med., 9:229, 1940.
8. Peters, G. A., and Silverman, J. J.: Role of histamine and acetylcholine in the mechanism of heat allergy. Arch. Int. Med., 77:526, 1946.
9. Segal, M. S.; Beakey, J. F.; Bresnick, E., and Levinson, L.: Evaluation of therapeutic substances employed for the relief of bronchospasm, preliminary note. Bull. New England M. Center, 10:21, 1948.
10. Segal, M. S.; Bresnick, E.; Beakey, J. F., and Levinson, L.: Evaluation of therapeutic substances employed for the relief of bronchospasm, VI. Antihistaminic agents. (In preparation.)

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1948-1949

Editorial

COLLEGE PROGRESS

During the past year the College has continued "blazing the trail." The Fifth Annual Session, the tentative program of which is included in this issue, is for the purpose of promoting and advancing the study, research, and clinical knowledge of allergy, and embraces fifty-four presentations including two symposia and animated and colored movies. In addition, there will be a half-day Panel Discussion on Pediatric Allergy, and twelve papers to be read *by title*. The papers are well balanced to include investigative research, clinical allergy, and the relation of allergy to public welfare. As a means of promoting cordial relations among those engaged in the practice of allergy, there will be the usual evening entertainment including the annual banquet, short speeches, a featured movie, and orchestral music for dancing.

The College, recognizing the importance of properly orienting psychologically allergic patients, initiated and published for the first time a Panel Discussion on "Psychodynamics and the Allergic Patient," as presented at the Third Annual Session of the College in Atlantic City, New Jersey, June 8, 1947. A second Panel Discussion held at the Fourth Annual Session of the College in New York City on "Otolaryngologic Allergy" will be published soon.

The College held a very successful 1948 Postgraduate Instructional Course in Allergy under the auspices of the University of Oregon Medical School with an unprecedented attendance. The promotion of friendly relations among those engaged in the practice of allergy throughout North and South America, as well as countries abroad, has been most encouraging.

The College is co-operating with interested allergy societies in every way in seeking an autonomous board of allergy.

The receipt of manuscripts for ANNALS OF ALLERGY, which is deeply appreciated, has necessitated enlarging the ANNALS to 184 pages, but so far, in spite of rapidly increasing cost, the subscription price has remained the same. We are grateful for the confidence of our Sustaining Members and of those who have continued their advertising in the ANNALS, regardless of adverse conditions. We are grateful to the publishers for their hearty co-operation and personal interest in promoting our publications. Last, but foremost, we are grateful to our entire membership which has furthered the progress and growth of the College by being ever loyal and co-operative in subscribing to its policies.

Progress in Allergy

THE MANIFESTATIONS AND MECHANISMS OF VASCULAR ALLERGY

A Critical Review

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The scope of this paper is a critical review of the literature bearing on the relation between allergy and vascular disease.

Though relatively few significant clinical and experimental observations have been made—largely during the last decade—there are many reports with reviews of the literature and restatements of the premise that necrotizing arteritis may be an allergic manifestation.

There would be slight justification for another review of the subject unless it included an attempt to inquire more thoroughly, and perhaps with a somewhat different perspective, into the question which must ultimately be answered—what are the fundamental mechanisms involved? I have felt free, therefore, to reach into related fields for data which seemed pertinent, and, in Section II, to propose a working theory of the mechanisms of vascular allergy.

I. MANIFESTATIONS OF VASCULAR ALLERGY

The inclusion of an ever-increasing number of clinical conditions into a group having a vascular allergic reaction as the common denominator has an interesting historical background. In the years 1895-1914 Osler wrote a series of papers[230-242] in which he presented the concept of a unified group of apparently unrelated diseases. This has been called the "erythema group" of Osler. A consideration of his papers shows that his first reports deal with the cutaneous and visceral manifestations of "erythema exudativum multiforme." Later he refers more broadly to the "erythema" group, and we can appreciate his statement[210] that "it was very difficult to find a name under which to group the cases."

Paradoxically, these observations gave rise to more precise definition of each syndrome so that the concept of a related group of diseases which were not necessarily identical was lost in the forest of classification. Furthermore, in spite of Osler's admission that he was primarily interested in similarities, he was criticized for not having recognized certain obvious differences. On the basis of these differences, it is often possible to distinguish one disease from another in this group. At times, however, even when the disease apparently fits into one syndrome, it may show many features which we associate with others. It is sufficient to cite just a few examples. Lamb[164] calculated that 39 per cent of his cases of periarteritis nodosa had severe migratory rheumatoid joint pains, while a few cases had erythematous or hemorrhagic skin lesions. An even more intimate association between periarteritis nodosa and rheumatic fever has been described.[91] Geipel[92] has reported occasional aneurysm formation in rheumatic arteritis. The case of scleroderma described by Banks[21] presented the usual clinical picture, but also had marked photosensitivity and skin pigmentation as well as acute arteritis in the kidneys. Masuri and Yaffe[213] also report a case similar to this. Finally, it is

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generally accepted that a case may begin as a typical disease of one type, only to present later the clinical and pathological picture of another. Thus features of scleroderma, dermatomyositis, and disseminated lupus may be seen in the same case. The difficulties of clinical classification in some cases have resulted in quite an array of syndromes being proposed[169] which are difficult to evaluate since they usually express the presenting or chief lesion rather than the entire picture. The following are only a few of the attempts to find suitable names for the "atypical" cases reported: "Non-bacterial thrombotic endocarditis,"[92] "erythema multiforme,"[214] "purpura,"[90] "periarteritis nodosa and rheumatic fever,"[91] "Pick's disease with polyarthritis and glomerulonephritis,"[308] "serositis and glomerulonephritis,"[58] "obliterating arteritis,"[22,23] "pemphigus and lupus erythematosus" (Senear-Usher syndrome),[98,289,301] and "chronic myositis."[237]

The overlapping of clinical syndromes is further confused by the lack of characteristic and diagnostic histopathological changes to correspond with the clinical syndromes. On the contrary, the pathologists feel that degeneration of collagen and vascular damage are probably common to the whole group.

This has naturally led some to again suppose that a common etiological denominator must be present. In two previous papers[218,219] we felt that it was not unwarranted to consider the group under the term of *"visceral angiitis."* It should be emphasized that this concept is useful only as an aid in the search for the common denominator, if any. It does not imply a disregard for the specific syndromes any more than the discovery of bacteria eliminated the differentiation of various types of infection. As a matter of fact, little therapeutic progress was made until the etiological agent was demonstrated.

With the above limitations on the use of this inclusive term, this review will consider in the *visceral angiitis group* the following conditions: *periarteritis nodosa, glomerulonephritis, rheumatic fever, lupus erythematosus, scleroderma, dermatomyositis* and *serum sickness.* Other diseases will be discussed which might have been included in the group, but it seems best to treat these separately until more evidence is available to justify inclusion.

Rokitanski[222] was probably the first to describe the clinical picture and gross pathology of the disease which Kussmaul and Maier[183] later named "periarteritis nodosa." There have been many speculations as to the cause of this spectacular disease which is characterized by widespread necrotic and inflammatory arterial lesions. Verse[318] associated it with syphilis, Harris[124] suggested a virus etiology, Benda[25] and Tschamer[309] refer to a vague concept of toxic injury and to the possible role of various infections, while Jores[156] blamed a specific, but unidentified, infectious agent. A relationship to tuberculosis has been suggested by the occurrence of necrotizing arterial lesions in tuberculous meningitis.[17,38,102] The relationship of periarteritis nodosa to streptococcal infections has been indicated by reports of cases which followed scarlet fever.[148,245] Wolbach[340,341] and Bennett[26] have pointed to the similarity between the vascular lesions in this disease and in Rocky Mountain spotted fever. Periarteritis nodosa has also been reported in association with trichinosis.[257]

In 1923 Gruber[114] suggested that this disease was a manifestation of hypersensitivity, but his paper contains little to support his perspicacity. Clark and Kaplan,[59] on the other hand, reported the observation at autopsy of lesions similar to periarteritis in two patients in whom serum sickness had developed shortly before death, but they were somewhat reluctant to point to a causal relationship between the serum sickness and the arterial lesions. In the same year Eason and Carpenter,[73] in discussing the treatment of rheumatic fever with anti-scarlatinal serum, reported that one of the patients so treated developed serum sickness and that the lesions of periarteritis nodosa were encountered at autopsy. Interestingly enough, they felt that the presence of known rheumatic fever made it difficult to evaluate the role

played by the serum reaction. Others were led by the tissue and blood eosinophilia to suggest a hypersensitivity reaction on the basis of the frequent association of eosinophilia with allergy.[191]

Although similar arterial lesions had been produced experimentally by several workers using various substances such as bacteria,[211] foreign protein plus streptococci[216] and egg albumen,[282] it remained for Rich and his co-workers to correlate the clinical, pathological and experimental data, and to present it in support of the hypersensitivity reaction. In 1942[259,260] he reported the finding at autopsy of acute arterial lesions similar to those of periarteritis nodosa in seven patients who had been treated with serum and sulfonamides. In one of these cases a biopsy taken before the onset of serum sickness had shown no arterial lesions, while tissues studied after did show typical arteritis. Later he reported a case[261] in which periarteritis nodosa was apparently due to sensitivity to iodine.

Experimentally, Rich and Gregory[267] injected horse serum alone and in combination with sulfadiazine into rabbits. Five to eight days after the injection of serum many of the rabbits developed an aural flush which faded after a few days. This has been described previously[84,116] as a hypersensitivity reaction. By the fifth or sixth day after serum was given, there was a marked rise in body temperature (104°-105.8°F.). On the twelfth day the animals had become skin hypersensitive. The skin reactions were characterized by prompt edema followed by large indurated erythematous lesions. Seventeen days after the initial reaction, 1 c.c. of horse serum was given intravenously with some fatalities due to anaphylactic shock, but the survivors received 10 c.c./kg. of serum intravenously two days later. These animals developed a high degree of skin sensitivity, showing hemorrhage and necrosis. All of the animals were finally autopsied. Histologically, eight out of nine of the serum-treated rabbits showed arterial lesions varying from simple edema to advanced medial necrosis and cellular infiltration. Four out of five of the rabbits treated with serum plus sulfadiazine showed the same lesions. Not always did the degree of vascular damage correspond to the dosage of sensitizing agent or to the degree of skin reactivity. It is noteworthy that in a few animals a single large dose of serum was able to produce arterial lesions.

Rackeman and Green[250] reported the coincidence of bronchial asthma and periarteritis nodosa in 12 per cent of their cases, while Wilson and Alexander[335] showed an even higher incidence. They collected 300 cases of periarteritis nodosa from the literature and found that in 18 per cent of the cases, asthma was also present, and that if one considered other allergic manifestations the figure would be nearer to 25 per cent. Harkavy,[120,121,122] in a study of a group of sixteen patients with bronchial asthma, showed that four of these patients were skin sensitive to the specific polysaccharide fractions of the same types of pneumococci isolated from the sputum. In these cases precipitins and agglutinins for the specific organisms could be also demonstrated. The skin reactions took the form of an immediate wheal followed by a delayed tuberculin type of reaction and were often associated with systemic manifestations such as generalized urticaria and asthmatic paroxysms. Two patients tested with autogenous vaccines showed an acute asthmatic paroxysm and severe anaphylactic shock, while a third showed severe cough, pulmonary infiltration and generalized hemorrhages. Four of the sixteen patients came to autopsy and showed arterial lesions in the peripheral arteries including the lungs, coronary arteries, and kidneys. This is a very important series of studies because of the conclusive demonstration of bacterial hypersensitivity in these cases.

Before going any farther, it seems advisable to attempt to reconcile the nomenclature and pathological classification of the arterial lesions. The term "periarteritis nodosa" introduced by Kussmaul and Maier[151] suggests a primary periarterial inflammatory reaction, followed by weakening of the vessel wall and aneurysm formation. The early human lesions, however, are primarily located in the media and intima;

there may be fibrinoid necrosis without striking cellular infiltration, and eventual aneurysmal dilatation is by no means a constant finding. The term "polyarteritis nodosa" introduced by Haining and Kimball[117] is an attempt to indicate that the arterial inflammation involves more than the adventitia, but still retains the "nodosa" part. It seems hardly justified, therefore, to substitute this for the original term when the clinical syndrome is being described.

There has been a great deal of loose use of the term "periarteritis nodosa," especially in reports of experimental work. It seems obvious that there is a significant difference between the statements that periarteritis nodosa has been produced and that lesions similar to those of this disease have resulted. Unfortunately these two claims have come to mean the same thing to many writers. It would be more accurate to refer to the production of "acute panarteritis" or "necrotizing arteritis." The same caution should be exercised when reference is made to lesions resembling those of other diseases in this group. The use of the term "visceral angiitis"[182,218,219] has already been defined. Harkavy's use of "hyperergic vascular disease" carries a more specific etiological connotation.

The claim of Smith and co-workers[299,343] that "periarteritis nodosa" can be distinguished from "hypersensitivity angiitis" is a good example of this confusion. In 1944 Smith, Zeek and McGuire[299] reported the production of "periarteritis nodosa" in animals made hypertensive by the silk peri-nephritis method. Later,[343] human cases were divided into two groups, those having no definite history of allergic manifestations (periarteritis nodosa) and those with preceding allergic histories (hypersensitivity angiitis). They then concluded that the lesions of "periarteritis nodosa" of rats and humans could be differentiated from "hypersensitivity angiitis" on the basis of the distribution of the lesions, the presence of various stages of development, involvement of pulmonary and splenic vessels, and predilection for arteries of different calibers. Most of these points can be challenged. In the first place, vascular necrosis is frequently seen in malignant hypertension,[181] and since aneurysmal dilatation is more likely in the presence of a weakened arterial wall plus hypertension[93,118,288,334] the lesions produced in their hypertensive animals are just as "like" periarteritis nodosa as the others reported. Their statement that in other reports on the subject "the identification of these lesions as those of periarteritis nodosa has not yet been proved" is certainly applicable to their own use of the term. There are other points of difference. In Rich's studies with hypersensitive rabbits, he states that "every stage of the process encountered in human periarteritis nodosa could be found in the various rabbits, and in the majority of the animals all stages were present in different arteries in the same rabbit." This is not in agreement with their conclusion that lesions of nearly the same age serve to define the cases due to hypersensitivity. The same can be said of the frequency of involvement of the pulmonary arteries. All in all, there is little justification for their suggested classification.

The next condition to be considered is acute glomerulonephritis. In 1913 Longcope[202] produced glomerular lesions by repeated injections of foreign protein into sensitized animals, and less marked lesions were described by Miura[223] in rabbits that had received large doses of foreign protein intramuscularly. Masugi and Sato[212] produced glomerular lesions in rabbits by intensive treatment with intravenous foreign serum. In the experiments of Rich and Gregory[268] seven out of nine rabbits receiving horse serum and three out of five receiving both serum and sulfadiazine showed lesions indistinguishable from the human lesions of acute glomerulonephritis. Their data shows that glomerulonephritis did not develop only in those cases where arterial necrosis of the renal arteries was present, suggesting that the glomerular lesions may not be dependent on the damage to arteries. Furthermore, the almost selective effect on endothelium of the glomerular capillaries in animals showing, in addition, diffuse visceral arteriolar damage indicates that

within the same body various tissues may have different reaction affinities and that endothelial damage may be just as significant as the gross arterial necrosis.

Schwenkter and Comploier[256] suggested some years ago that kidney antibodies might play a role in the production of glomerulonephritis, while Smadel[296a] has produced glomerular disease with specific nephrotoxic sera. The recent work of Cavelti[50-56] is a novel and promising approach along these lines. By using a collodion particle technique to determine antibody titers, he has shown that high titers of autoantibodies to kidney, heart, and connective tissue can be produced in rats and rabbits by immunizing a given animal with mixtures of killed streptococci and emulsions of the homologous tissue. Staphylococcus toxin can be substituted for the killed streptococci, but the presence of one of the bacterial preparations is required, for the homologous tissue by itself was shown to be inactive. Significant antibody titers were obtained, in one rabbit as high as 1:40,960, and the interval between immunization and the appearance of antibodies varied in different animals from four days to several weeks. Of sixty-one rats showing kidney antibodies, forty-four showed renal lesions, and, in general, the more severe reactions were observed in animals having the highest titers. Occasionally, however, as in Rich's experiments with foreign serum, a single injection of streptococcus-kidney antigen was sufficient to produce renal lesions.

In rats, the urinary findings in the acute phase consisted of proteinuria, cylindruria, hematuria, and the presence of desquamated tubular cells. The majority of the casts were of the cellular and granular types, but in some cases hyaline casts were also present. In the subacute and chronic phases, the urine characteristically revealed a progressively more severe proteinuria plus casts of the hyaline and granular type. Microscopic hematuria was present in most cases. Gross examination of the organs during the acute phase showed the kidneys to be swollen and edematous and the heart weights to be significantly increased in about half of the animals. In the subacute and chronic phase there was a more marked increase in kidney and heart weight. The damage during the early phase appeared to be primarily to the glomeruli with very little alteration of the tubules and interstitial tissues. The photographs of the glomerular lesions so produced support the statement that they are indistinguishable from those of human glomerulonephritis. It is interesting that although rabbits similarly treated developed amyloidosis, they did not show the lesions of glomerulonephritis seen in rats.

Cavelti's observation that rats do not develop antibodies to kidney when homologous kidney emulsions alone are injected appears to be at variance with the production of high titers when heterologous tissues are used. For example, Miale[217] showed that injection of emulsions of dog heart, spleen, or bone marrow emulsions into rabbits produced significant titers of specific antibodies and that these rabbit antisera apparently had a specific effect when injected into dogs. The required presence of killed streptococci or straphylococcus toxin when homologous antigen is used may be explained by Cavelti's suggestion that the antigen is the haptene and the bacterial substance the carrier. It is likely that the combination of homologous haptene with a foreign protein is necessary for the tissue emulsion to be as active as heterologous antigens. In this connection it should be noted that Smith and Zeek[278] found that necrotizing arterial lesions occurred in the majority of unilaterally nephrectomized animals in which the silk around the remaining kidney was infected with staphylococci, streptococci, and Salmonella, whereas the introduction of silk and organisms into the peritoneal cavity at a distance from the kidney failed to produce vascular necrosis.

A consideration of the relationship of rheumatic fever to the visceral angiitis group leads us over the same type of evidence considered above. Klinge,[177] Vaubel,[314] and Jungbauer[177] found lesions resembling those of rheumatic fever in the coronary arteries of animals sensitized to horse serum. Gross,[115] however,

agrees with Brunn[42] that these demonstrations are not entirely convincing. The relationship of streptococci to rheumatic fever has been investigated rather thoroughly,[220,233] and there is more agreement than disagreement with the belief of Swift[302] and Coburn[60] that rheumatic fever is basically a reaction to streptococcal infection.[4] The immunological tests using streptococcus purified substances for skin testing have given equivocal results, which at the present state of knowledge does not necessarily eliminate a streptococcal etiology. Wedum[328] was able to demonstrate that an antigenic substance was present in the blood during the pre-rheumatic phase, and that specific antibody appeared at the onset of the rheumatic attack. This certainly needs confirmation and elucidation. An allergic predisposition is suggested by the survey of Rittwagen et al[273] which shows that rheumatic children have three times as high an incidence of clinical allergy as non-rheumatic controls.

In the experiments of Rich and co-workers cardiac lesions bearing a striking resemblance to those of rheumatic carditis were found associated with the arterial and renal lesions already described. Rich points out[268] that the experimentally produced lesions are fundamentally similar to the generally recognized changes in human cases, consisting of focal edema of the connective tissue with swelling and degeneration of the collagen fibrils, inflammatory pericardial, valvular and mural infiltrations with characteristic preference for the valves, and lastly, perivascular infiltrations in the connective tissue septae. The lesions produced by Cavelti[50,53] were chiefly valvular and interstitial. The histopathological similarities between human and experimental lesions and between these and the findings in known allergic states are certainly impressive. The focal connective tissue injury characterized by edema and degenerative changes in collagen fibers seen in rheumatic fever certainly resembles closely the change seen in severe local anaphylactic reactions. The arterial changes in rheumatic fever have been fully described,[15,95,162,233,244,320,] and the acute lesions present the same picture of a severe vascular reaction as is described in sulfonamide sensitivity.[35,39,87,103,197,226,300] Interstitial eosinophilic infiltrations in the heart are encountered in human cases of rheumatic fever,[15,16,228,325] in the experimentally produced lesions, [152,268] and in cases of sulfonamide reactions in humans,[88,192] while blood eosinophilia has been described in chorea[27] and of course in serum sickness and other allergic reactions. Purpura is occasionally seen in acute rheumatic fever[60] and in anaphylactic reaction,[5,249] while the association of thrombocytopenic purpura with endocarditis has been reported by Friedberg and Gross.[90]

The clinical resemblance of acute rheumatic fever to serum sickness is well known. Both are characterized by fever and arthritis, and occasionally there is seen an indistinguishable skin eruption in both conditions. There are other similarities. Transient paresis is occasionally seen in rheumatic chorea and also during serum sickness,[258] while occasional instances are recorded of choreiform attacks in the course of serum sickness. Lastly, many cases of serum sickness show transient cardiac abnormalities, such as Adams-Stokes syndrome[66] and electrocardiographic abnormalities.[86,323] Boas[37] reports a case of coronary thrombosis after serum administration. Wilcox and Andrus[331] have described lengthening of the P-R interval and abnormal QRS complexes and T waves in guinea pigs sensitized with horse serum. Similar electrocardiographic changes have been noted during anaphylactic shock.[49] While not conclusive, these findings cannot be lightly dismissed.

In the 1946 Harvey Lecture, Rich[262] points out that in common with rheumatic fever, periarteritis nodosa, and serum sickness, lupus erythematosus may present fever, urticaria, erythema, purpura, arthritis, acute panarteritis, degeneration of collagen, focal necrosis of lymph nodes and spleen, myocarditis, valvulitis, serositis, and pneumonitis. One of his studies[269] illustrates the similarity of the experimentally produced lesions to those in human cases. Rost[278] also discusses the possibility

that lupus erythematosus is a systemic allergic disease, while Fox[85] describes a case which followed serum sickness.

It is agreed that lupus erythematosus is a systemic disease which shows characteristic skin lesions in some cases.[100,151,161,165,166,167,246] The verrucous endocarditis described by Libman and Sacks[196] and now widely referred to as the Libman-Sacks syndrome pointed to the cardiac involvement. With the added observations of Gross[111,112] cardiac damage has come to be accepted as a frequent finding.[150] In a classic study, Baehr, Klemperer, and Schiffrin[18] called attention to the diffuse vascular lesions and to the frequent involvement of serous surfaces, and suggested that the widespread endothelial damage indicated an "endotheliotropic injurious factor." The systemic nature of the disease was confirmed by others,[68,153,277] and characteristic lymph node[99] and pulmonary[251] lesions described. The full picture of the histopathology as presented by Klemperer, Pollack, and Baehr[176] was interpreted as a disseminated focal "fibrinoid" degeneration of collagenous fibers. This fibrinoid degeneration refers to the physicochemical change in collagen fibers which causes them to take on the staining characteristics of fibrin, but aside from this histochemical change, little is known about the nature of the degeneration. Fibrinoid degeneration is also present in rheumatic fever, in periarteritis nodosa, scleroderma,[29,213,247] and in experimentally produced vascular lesions.[97,178] Nevertheless, Klemperer feels[175] that because fibrinoid degeneration is seen in other (apparently) unrelated conditions, because the cellular exudate differs somewhat, and because there is little direct clinical evidence that an allergic state is present in lupus erythematosus and scleroderma, definite inclusion of these conditions into the more clearly substantiated group of periarteritis and serum sickness is not warranted.

There are many who disagree, some even with the morphological interpretation. For example, Rich[262,269] feels that the sclerotic arterial lesions produced in the sensitized rabbit are indistinguishable from the sclerotic lesions in human cases of lupus erythematosus. Stickney and Keith[301] disagree with Klemperer's view that there are pathognomonic histological lesions in lupus erythematosus.

Without denying the importance of the contributions of anatomic pathology, it seems proper to suggest here that there is a measure of logical incompatibility to attaching too much importance to anatomical detail while at the same time searching for a common denominator. This applies to both the studies on humans and the observations of the histology of various experimental lesions. The premise seems clearly defined, that if a common pathogenesis exists, the measure of reactivity is not always predictable, and therefore may be similar but must not necessarily be identical. If hypersensitivity is the common denominator, then it is the similarities which are important, rather than the differences, at least until we understand better the nature of allergy. When we know why the same antigen in the same person can produce a great variety of reactions at different times, we may be able to reconcile the anatomical differences.

Furthermore, it is difficult to accept the statement that no allergic background exists in lupus erythematosus in the face of the frequent occurrence of photosensitivity of the skin.[43,256,276,285,306,310,324,339] Even in cases where the lesions are primarily visceral, photosensitivity without porphyrinuria is seen.[61] In about one half of their cases, Ludy and Corson[208] demonstrated hematoporphyremia and porphyrinuria, and feel that ultraviolet light in constitutionally susceptible persons is a factor. We are still far from understanding the nature of physical allergy, and for an appraisal of the present state of knowledge Epstein's reviews[78] may be referred to. We might refer however to the coincidence of hematoporphyrinemia and arterial lesions in lead poisoning,[278] and to Fahr's report[80] of cases of dermatomyositis occurring in lead workers. A very interesting cure of severe light

sensitivity after cholecystectomy recently reported[314] suggests that infection may play an important role.

A second chemical change seen with great regularity in lupus is hyperglobulinemia. It was present in 100 per cent of the cases of lupus erythematosus studied by Coburn and Moore,[61] and they showed that it was due to an increase in gamma globulin. Kagan[160] presents data showing that hyperglobulinemia is seen also in periarteritis nodosa, rheumatoid arthritis, acute glomerulonephritis, diseases of the bone marrow, and in chronic infectious diseases. The production of globulins, it is generally agreed, is a function of the plasma cell and the reticuloendothelial system.[30,31,82,83,238,305] Huebschman[149] called attention to the plasmacytosis in spleens of patients dying of chronic infectious diseases and suggested that the plasma cell produced antibodies. Markoff,[210] Gormsen and Heintzelmann[104] have described hyperglobulinemia and bone marrow plasmacytosis in patients with serum sickness. Experimentally plasmacytosis and hyperglobulinemia have been produced with tuberculoprotein,[69,221] horse serum,[263,364] streptococcus viridans[179,180,181] formalin killed pneumococci[32,33,34] and egg albumen.

A third group of observations indicate a possible relationship of disseminated lupus erythematosus to the visceral angiitis group. In 1943 Krupp[182] reported the occurrence of an unusual and probably characteristic urinary sediment in two-thirds of his cases of visceral angiitis, characterized by the simultaneous presence of elements usually characteristic of the early stages of nephritis (erythrocytes and erythrocytic casts) and those usually seen in the chronic stage (broad casts, waxy casts, fat casts, and "oval fat bodies"). This was confirmed by Miale[218] in a smaller series of cases of periarteritis nodosa and lupus erythematosus, and he showed that this typical sediment was characteristic of the acute stage of the disease. The urinary findings recorded by Cavelti in the rats treated with rat kidney and killed streptococci are suggestively similar. It is hoped that investigations of the urinary sediment by qualified observers will reveal these findings to be less unusual than the "routine" reports would indicate.

It is well known that transient pulmonary infiltrations are seen in the course of the diseases discussed above as well as in other allergic manifestations.[62,120,317] The nature of these infiltrations in asthmatics appears to be of several types. The first is not related directly to the allergic reaction and is often seen in cases of bronchial asthma on the basis of localized bronchiolar obstruction, atelectasis, invasion of pyogenic bacteria and the production of patches of bronchopneumonia. However, in some cases of bronchial asthma described by Harkavy[122] there seemed to be the added component of congestion, edema and thrombosis of small vessels, while one of his cases showed infiltration of the interalveolar septae with eosinophils, polymorphonuclear leukocytes and lymphocytes. One case described by him showed arterial lesions characterized by intimal thickening, in another there was a necrotizing arteritis with perivascular eosinophilic infiltration, while a third showed endarteritis. This second type of pulmonary involvement in allergic diseases resembles the syndrome described by Löffler.[199,200] The clinical picture has been well described and needs no discussion.[28,119,258,332] Autopsy studies such as those of vonMeyenburg[321] and of Baggenstoss, Bayley, and Lindberg[19] show the main features to be a predominance of eosinophilic leukocytes in the pneumonic exudate as well as bronchial, peribronchial and perivascular eosinophilic infiltration. There are also focal granulomatous lesions and necrotizing arteritis and arteriolitis. The pulmonary lesions have been reproduced experimentally in rabbits.[130] Bergstrand[28] emphasizes the similarities of this syndrome to rheumatic arthritis, periarteritis nodosa and allergic phenomena. That it may be associated with hypersensitivity to parasites is shown by its occurrence in pulmonary infestation by Acarina mites.[48,315]

The third type of pulmonary lesion is associated with rheumatic fever and is

generally called "rheumatic pneumonitis." This has been adequately described by many authors.[74,76,105,106,230] Rich and Gregory[270] emphasized that the basic lesion is focal necrosis of the alveolar capillaries with thrombosis followed by organization of the hemorrhagic foci to form the Masson bodies which are characteristic but not pathognomonic of the later stage. In some patients focal pulmonary lesions developed during treatment with sulfanilamide derivatives,[35,87,192,197,215,226265] In 1946 Gregory and Rich[109] described the same type of lesion in the lungs of rabbits with experimental serum sickness.

It seems to me that one of the most fundamental points in the consideration of these hypersensitivity reactions is the question of why the lesions are in some cases found exclusively or predominantly in a certain organ. In Löffler's type of pulmonary infiltration the lesions are limited to the lungs, but in other allergic states such as angioneurotic edema, pulmonary involvement is not uncommon.[62,317] Old and Russell[232] report an extremely interesting case of necrotizing arteritis limited to the lungs of a young boy whose heart had a large interventricular septal defect with right-sided hypertrophy and dilatation. They suggest that the increased pulmonary blood flow produced a relatively higher concentration of the toxic substance in the lungs than elsewhere. The local concentration of antigen and antibody is certainly important,[67] but the pulmonary hypertension is probably more significant, as suggested by the development of atheromatous lesions in the pulmonary arteries of human cases having increased pressure in the pulmonary circuit.

The vascular system also shows varying localization of the lesions. For example, Harkavy[122] relates angina pectoris to hypersensitivity to tobacco, whereas in other cases the chief manifestation seems to be thromboangiitis obliterans. He also records[123] various types of cardiac arrhythmia as a result of hypersensitivity to foods, but in two patients migratory phlebitis of the legs was the only manifestation of hypersensitivity to fish. Duke[72] describes extrasystoles, tachycardia, and angina pectoris as the result of heat and cold hypersensitivity. Even in drug hypersensitivity in which skin manifestations are the rule, it is possible to have cardiac involvement which is more severe than the skin reaction.

The kidneys are frequently involved in the diseases of the visceral angiitis group. According to Arkin[9] renal involvement occurs in 88 per cent of the cases of periarteritis nodosa. In experimentally produced "cortical necrosis of the kidneys" [36,96] diffuse arterial involvement in other organs is often described, whereas in human cases the damage is primarily to the renal vessels.[41,71] The renal damage of sulfonamide sensitivity does not as a rule spare the arterioles, but occasionally produces such a marked interstitial reaction[87,226] in the absence of striking arterial lesions that preference for capillary endothelium must be assumed. Kimmelstiel[170] refers to this acute interstitial nephritis as an "allergic hyperergic reaction."

It has been proposed by some[6] that the necrotic inflammatory lesions localized to the temporal artery in the clinical syndrome called "temporal arteritis[20,143,144,145,154,269] are hypersensitivity reactions. The relationship to allergy is not definite, but it may represent the highest possible degree of localization of an arterial lesion

The conditions existing in pregnancy would seem ideal for the production of allergic reactions in both the mother and the fetus. Isoimmunization to Rh antigens and possibly to other group specific substances produces erythroblastosis in the fetus. Although in this condition capillary endothelium is probably the chief site of involvement, it appears nevertheless to be a severe vascular reaction. Wilmer[317] describes two cases of periarteritis nodosa during the first year of life. One of the cases occurred in an eleven-day-old infant with an umbilical infection. On the basis of Ratner's studies[273,274,275] showing that the guinea pig fetus can be sensitized either by injecting the antigen into the mother or by adding it to her diet, the suggestion is made that the arterial lesions may have developed in utero. The

concommitant infection in this case is interesting when considered in the light of the discussion in the second portion of this review.

In the mother, toxemia of pregnancy has been related by some to sensitization to placental substances. Yamada[342] found that a small amount of protein prepared from eclamptic placentas was able to produce severe contractions of isolated uterine muscle strips of guinea pigs sensitized to eclamptic serum. Seegal and Loeb[287] injected pregnant rats with rabbit anti-placenta serum and noted that abortion usually followed. Lin[198] sensitized rats with placental protein and then allowed them to become pregnant. Most of the rats developed moderate albuminuria, hypertension, and edema. Thickening of the arteriolar walls and of the basement membrane of Bowman's capsule in the kidneys was noted histologically. These studies suggest a promising approach to the study of toxemia of pregnancy. The studies of Apitz[7,8] in which he produced cortical necrosis of the kidneys by injecting a single dose of bacterial filtrate intravenously into pregnant rabbits points to pregnancy *per se* as being a possible blood vessel sensitizer. The occurrence of cortical necrosis in human pregnancies has long begged for an elucidation of the mechanism by which it is produced.

It is hoped of course that a better understanding of the fundamental processes involved in visceral angiitis will eventually indicate a course of rational therapy. The work to date suggests only two types of treatment. The first is directed at the allergic nature of the disease, and consists of specific (or nonspecific) "desensitization" or in the use of the "antihistamine" drugs. A discussion of this does not fit into this review.

The second approach to therapy involves the possible use of the tocopherols (vitamin E). A voluminous literature has already accumulated on vitamin E, most of it dealing with biochemical studies. The reports on the effect of vitamin E deficiency present a bewildering number of physiological abnormalities in different species, and only articles pertaining to this review will be considered.

The tocopherols are naturally occurring phenolic antioxidants. All of the naturally occurring antioxidants occur in plants, and, except for cephalin, cannot be synthesized in the body. In vegetable tissues the highly unsaturated fatty acids are protected from auto-oxidation by the antioxidants and associated stabilizers.[181] We do not know as yet whether in animals this protective function is quantitatively as important as in plants, but it is known that a high intake of unsaturated fatty acids is necessary along with reduced vitamin E intake to produce vitamin E deficiency. In any case, the antioxidant effect *in vitro* and *in vivo* appears to have been satisfactorily demonstrated.

In 1942 Pappenheimer[243] reviewed the structural and functional muscle abnormalities induced by vitamin E deficiency, and showed that paralysis paralleled structural and chemical changes. Whether vitamin E governs muscle metabolism directly or indirectly is still unsettled,[24,107,146,147,164,227] but it is of interest that tocopherol is effective in preventing nutritional muscular dystrophy, and in some cases a therapeutic effect has been noted. In cardiac muscle vitamin E deficiency in cattle produces electrocardiographic abnormalities and death due to heart failure.[115]

Of even greater interest are the series of studies by Holman.[133-140] He has shown that by controlling two factors, diet and renal insufficiency, arterial lesions were produced in dogs. The lesions consisted of a necrotizing arteritis affecting with great regularity the aorta, coronary arteries, pulmonary arteries, and auricular endocardium. The lesions, although unlike those of arteriosclerosis, resemble the arterial lesions of visceral angiitis in that collagenous necrosis is a fairly constant finding. The dietary factor is contained in, but is not unique to, cod liver oil and appears to be related to the unsaturated fatty acids. The renal insufficiency can be produced by several means. It is of interest to note that cod liver oil injury to the heart has been described previously.[2,3] The inference is that toxic lipids (probably

unsaturated) cannot be excreted by the kidneys and may produce arterial lesions. In this connection, it is interesting to note that Henning[129] has demonstrated sensitization to autogenous lipids. Recently Holman showed[138] that mixed natural tocopherols when given by mouth to the experimental animals were able to prevent the occurrence of arterial lesions.

Three general methods have been used to produce necrotizing arteritis in experimental animals. The first is by foreign serum, drugs, bacterial antigens, et cetera. The second is by producing hypertension. The third is Holman's dietary factor in the presence of renal injury. A lengthy discussion of the theoretically possible relationships, if any, among the three would certainly be pure speculation and unwarranted at this time. However, some points of interest are obvious. The first is the frequent involvement of the kidneys with severe renal insufficiency in the visceral angiitis group, which leads us to wonder whether one can exclude retention of toxic lipoid materials as a primary or adjuvant necrotizing factor. The second is the relationship of Holman's findings to the necrotizing arteritis produced in hypertensive rats. The third is the nature of the vascular damage in arteriosclerosis in which renal insufficiency is common. Lastly, there are clinical reports of the therapeutic values of tocopherol in human vascular disease, such as that of Shute et al[291] and more recently of Burgess.[44] These should be considered preliminary reports, and both are rather superficial. Nevertheless, Burgess reports that clinically a favorable response was noted in some of the diseases of the visceral angiitis group following the administration of vitamin E in adequate doses.

II. MECHANISMS OF VASCULAR ALLERGY

Almost without exception the numerous writers on necrotizing arteritis repeat the statement made by Rich[259,260] that the vascular damage is similar to that seen histologically in the Arthus phenomenon. Although there is no denying the similarity, the implication that this is the basic mechanism has generally excluded a consideration of other types of allergic reactions. Indeed, it would be tempting to let the matter rest with that.

There are many questions which must be raised. The Arthus type of reaction represents a much less frequent mode of response than those seen in bacterial hypersensitivity and immunity. The production of acute arteritis by drugs and other foreign agents to which there has been no previous exposure or sensitization does not appear to bear any relation to the conditions of the Arthus experiment. Also, there seems to be no good reason for the general failure to consider the possible role of the Sanarelli-Shwartzman reaction, especially in cases preceded by bronchial asthma and bacterial infections or in cases where the necrotizing arteritis is localized primarily in one organ. Why there should exist any preferential distribution of lesions in certain organs and why arteries and capillaries should be more severely involved than veins are also interesting questions. What role, if any, antiallergens, isoimmunization, and blocking antibodies play must be considered. Much work remains to be done before these points can be cleared up, but ultimately these and many other questions must be answered if the concept of vascular allergy is to have acceptable support. It is hardly sufficient to group a number of disease states merely on the basis of a common pathological lesion resembling that seen in one of the allergic phenomena.

In 1903 Arthus[13,14] reported that rabbits did not react to a single injection of horse serum, regardless of the route of administration, but that if the serum was injected subcutaneously at six-day intervals, a prompt local reaction occurred after four or five doses. This consisted grossly of edema, infiltration, and necrosis, while microscopically there was necrosis of capillaries and terminal arterioles, interstitial edema and hemorrhage, and cellular infiltration. Detailed histological studies by Gerlach,[97] Opie[234,236] and others have confirmed the essentially vascular

nature of the reaction. It should be emphasized that his hyperergic response reaches its maximum in about twenty-four hours, that it is a manifestation of protein sensitivity in most cases, and that while some animals, like the rabbit, are particularly suitable for demonstrating it, in other species it cannot be elicited regardless of the quantities of antigen given. This last observation is often quoted by those who are reluctant to accept the concept of an allergic background for vascular disease. However, both species and organ specificity must be better understood before much emphasis can be put on this point of disagreement. For example, it has been shown[125a] that rats vaccinated with killed tubercle bacilli fail to show a skin reaction yet react violently if tuberculin is injected intra-abdominally. It is theoretically possible therefore for the blood vessels of some species to be as unreactive as the skin of rats.

The hypersensitivity which results from sensitization to bacteria is usually pointed to as being of a different nature. However, as Scherago[283] points out, there are several types of reactions in bacterial allergy, and a careful definition of terms is necessary. He classifies the hypersensitive reactions which may develop when tissues are brought in contact with bacteria into five types: (1) bacterial anaphylaxis (including toxin hypersensitivity), (2) bacterial atopy, (3) tuberculin-type hypersensitivity, (4) the Shwartzman reaction, and (5) bacterial heterophile toxicity.

There are said to be very fundamental differences between the Arthus type and the bacterial type of hypersensitivity, especially the tuberculin-like reactions. Rich and Lewis,[271,272] Aronson[10,11,12] and Moen and Swift[224] have shown that cells from tuberculous guinea pigs die on contact with tuberculoprotein, indicating a true cellular sensitization. In the Arthus type of hypersensitivity, however, Aronson[10] showed that there was no sensitization of extravascular tissues. Rich and Follis,[266] in a study of the site of sensitivity in the Arthus phenomenon, showed that the corneal tuberculin reaction in tuberculous guinea pigs consisted of marked necrosis of corneal cells, edema and leukocytic infiltration. This represents cellular necrosis in an avascular tissue, and confirmed the results obtained by Holly[132] and others. In the Arthus type of hypersensitivity produced in rabbits, the intracorneal injection of a drop of the foreign serum produced only minimal inflammatory changes in spite of the fact that 0.1 c.c. of serum intracutaneously produced a typical necrotic response. The same experiment done on vascularized corneas (by using a heavy suspension of heat-killed tubercle bacilli as an irritant) of Arthus-sensitized rabbits showed the development of capillary hemorrhage in twenty-four to forty-eight hours, with necrosis of corneal cells only in the vicinity of the hemorrhages. Assuming then that the reactions in the guinea pig and rabbit corneas are comparable (rabbits are much more susceptible to Arthus sensitization), that the somewhat delayed and less marked reaction of the vascularized cornea is comparable to the typical skin lesion, and that the use of killed tubercle bacilli to bring about vascularization of the cornea does not alter the reactivity of the capillaries to the foreign serum, it would seem that an essentially vascular effect in the Arthus phenomenon had been demonstrated.

Abell and Schenk[1] were able to demonstrate the vascular shock directly in rabbit's ears by observing the anaphylaxis in transparent chambers. Roessle[274] described the local anaphylactic reaction of the blood vessels in the mesentery of sensitized frogs. There is capillary dilatation and increased permeability with marked diapedesis and interstitial edema, but no tissue necrosis is produced in the frog, so that this resembles the anaphylactic wheal more than the Arthus phenomenon. The vascular reaction has been observed directly in chick embryos. Szepsenwohl and Witebsky[303] showed that three-day-old chick embryos contain Forrsman's antigen and that the vessels shrink when Forrsman's antiserum is applied directly. Later the embryo turns and sinks and total stand-still of the heart occurs. Wittich[337]

demonstrated the same sequence of events in eighteen-day-old embryos. Cannon, Walsh and Marshall[45] instilled purified egg albumin intranasally into egg-sensitized rabbits and produced an acute pneumonitis characterized at first by increased capillary permeability and later by acute arteritis, phlebitis, and thrombosis.

There is no doubt therefore, that in an animal sensitized with a foreign protein a state of allergy can develop in which the vascular system shows a particularly severe type of reaction. It would appear that an almost specific sensitization of the blood vessels had taken place, since *in vitro* extravascular tissue shows no necrosis. And yet, in this type of sensitivity it is also possible to demonstrate circulating antibodies and to effect passive transfer, indicating that there is still a great deal of circulating antibody. Why then should a fairly long incubation period be necessary before even the earliest vascular lesions make their appearance? If a minute amount of the antigen is given intravenously, typical anaphylactic shock is produced. This reaction is immediate, the manifestations being the same as those seen in bacterial anaphylaxis, in which passive transfer of antibody has not been demonstrated. On the other hand, in anaphylactic shock of the tuberculin type of bacterial hypersensitivity, the symptoms appear only after some hours and progress relatively slowly, but cells from an animal showing this type of hypersensitivity are killed rapidly when tuberculoprotein is added to them *in vitro*,[10,11,12,271-272] and although passive transfer with serum cannot be demonstrated, it may be produced by using the sensitized cells. This has been accomplished by Chase[57] who injected into normal guinea pigs cells from peritoneal exudate, spleens, or lymph nodes of tuberculin-sensitive animals and was able to demonstrate skin hypersensitivity of the tuberculin type in the recipients. This passive transfer has also been accomplished by Kirchheimer and Weiser.[171] Lastly, in the heterophile type of hypersensitivity, the systemic and cutaneous reactions resemble the Arthus phenomenon as far as the vascular damage is concerned, but no uterine muscle sensitivity can be demonstrated and desensitization has not been accomplished.

Since, then, we have on the one hand evidence of apparently fundamental differences in the various hypersensitive states, especially between the Arthus and the tuberculin types, and on the other the clinical and experimental evidence that vascular necrosis is produced not only by foreign serum, but by drugs and bacteria as well, there is much here to be reconciled. In addition, a vascular component cannot be excluded in any of the allergic reactions except possibly for contact dermatitis of the "epidermitis" type.[77] As far as the intensity of the reaction is concerned, in atopic dermatitis one may elicit a series of reactions of various intensity of which the most severe is the purpuric lesion characterized by necrosis of capillary walls and interstitial hemorrhage. Furthermore, the vascular necrosis in the Shwartzman phenomenon, which will be discussed later, is just as intense as that seen in purpura and in the Arthus reaction.

One of the factors which appears to determine the intensity of the reaction is the quantitative relationship between antigen and antibody. Of the many studies on this subject it is sufficient for our purpose to review briefly the work of Kabat and co-workers.[158,159] They showed that intravenous administration of 0.03 mg. of rabbit antiovalbumin N or Type III antipneumococcal antibody passively sensitized a 250 gm. guinea pig so that death resulted from anaphylactic shock when 1.0 mg. of the protein antigen or 0.1 mg. of the polysaccharide was injected intravenously. The same results were obtained with guinea pig antibody. The injection of as small a dose as 0.005 mg. antibody nitrogen produced severe systemic reactions in one third of the guinea pigs receiving 1 mg. of antigen intravenously. If a larger amount (0.04 mg.) of antibody was used for sensitizing, the amount of shocking antigen could be reduced to 0.1 mg.

In a subsequent study Fischell and Kabat[81] showed that the intensity of the Arthus reaction was dependent on the amount of antibody available at the site of

contact with the antigen. A given quantity of antibody (25 micrograms) injected locally produced the same degree of reactions whether the antigen was administered locally or intravenously, but if the antibody was given intravenously, twenty to forty times as much was required (1 to 2 mg.) to give the same degree of reaction. Furthermore, following intravenous administration of antibody, injection of antigen at several sites reduced the severity of the reaction at each point, suggesting widespread fixation of antibody. Minimal Arthus reaction required intracutaneous administration of 25 micrograms of antibody N, as compared with 0.01 micrograms of antibody N sufficient to sensitize guinea pig uterus directly. It appears that many times more antibody is required for an Arthus reaction than for a local anaphylactic response, and that the severity of the reaction is directly proportional to the amount of circulating precipitin.[47,63,94,235]

From the quantitative standpoint, therefore, it would seem that at least one of the factors involved in the production of violent reaction phenomena is an excess of antibody. The quantitative relationships would of course be altered if there should be local fixation of antigen or antibody, but even so the amounts involved in this case are very small. This has been demonstrated by Wittich[338] by neutralization tests on the skin of cattle. It seems very possible that our inability to demonstrate circulating antibodies in some allergic states is due, for one thing, to lack of sufficiently sensitive tests. Recent advances in methods of antibody titration[46,52,126,127,128] offer hope that this may eventually be confirmed. Zinsser[344] even suggested that quantitative effects might explain the apparent differences between immune antibodies and allergic antibodies. Arguments for this case are presented by Bronfenbrenner.[40]

Even if the difficulties of quantitative antigen and antibody determinations should be finally overcome, there is a second obstacle to our full understanding of some of the reactions. It is generally agreed that the determination of precipitation and flocculation phenomena *in vitro* do not necessarily correspond to the process which occurs *in vivo,* and that skin reactivity is not always a measure of hypersensitivity. Without entering into the argument of the importance of precipitation phenomena of antigen-antibody union, it must be pointed out that antibody may be produced which is not immediately precipitable, and may even be of the "blocking" type. That antibodies of this type are produced in human isoimmunization to an Rh positive fetus has been amply demonstrated.[195,248,329,330] It should be noted that this isoimmunization is brought about by long exposure to the antigen, and that the violent reaction does not take place until near or at the end of pregnancy. Blocking antibodies have also been noted in chronic brucellosis[110] or when the route of the antigen administration is altered.[307] Studies by Loveless on pollinosis[204-207] have emphasized the importance of neutralizing antibody. In addition, the *in vitro* modification by heat of antibodies from precipitating to blocking and back to the precipitating type, as demonstrated by Kleczkowski,[172,173] suggests a much more fluid system than we might anticipate. Further support is given by *in vitro* antibody modifications by means of photo-oxidation[311,312] and extraction of lipids.[125,141,142] Even more striking is Kleckowski's demonstration[174] that the complexes between human and horse albumin could be produced by heat denaturation which were precipitable by the antisera to either human or horse albumin. When excess human albumin was present, the complexes precipitated human albumin antibodies, whereas they combined with horse albumin antibodies without precipitation.

As was our purpose then, we seem to have arrived at a point far removed from the rigidly set up criteria for the Arthus experiment. A consideration of the Sanarelli-Shwartzman phenomenon would seem to be the logical last step.

In 1924, Sanarelli[280] injected rabbits intravenously with sublethal doses of living cholera bacilli. Twenty-four hours later he gave a second intravenous injection, and this produced fatal hemorrhagic lesions in the intestine, mesentery, and kid-

neys. In 1928 Shwartzman[292] injected B. typhosus culture filtrates intradermally into rabbits, and twenty-four hours later a severe hemorrhagic reaction appeared at the site of the intradermal injection, characterized by vascular necrosis and thrombosis and necrosis of tissue.

In spite of Schwartzman's belief[293] that his reaction is different from that reported by Sanarelli because of the possible effect of living bacilli on tissues in the latter, it seems probable that the two are closely related if not identical.[108,281] Because of this and observations to follow, historical correctness dictates that the local or systemic "preparation" of tissues by bacteria and their products be called the *Sanarelli-Shwartzman phenomenon.* Two of the characteristic features of the reaction are that the second (provocative) injection must be given intravenously and that different and immunologically unrelated organisms may be used for the two injections.

When both the preparatory and the provocative injection are given intravenously[7,8] visceral lesions are produced consisting of vascular necrosis. Gerber[96] confirmed these findings and added other significant observations. The renal lesions, consisting of local or diffuse cortical necrosis, showed a necrotizing arteritis of the interlobular arteries, usually involving the artery in a patchy fashion and sometimes extending to the afferent arterioles of the glomeruli. Black-Schaffer, Hiebert, and Kerby[36] showed that both washed meningococci and the culture filtrate could produce the necrotic reaction. In this study, meningococcemic purpura, the Waterhouse-Friedricksen syndrome, and cortical necrosis of the kidneys was produced, in addition to scattered vascular and necrotic lesions in the lymphatic system, myocardium, liver, and lungs. The vascular lesions have also been produced in a single organ by preparing it via its blood supply[294,295] or by interstitial injection.[108,228,163]

Shwartzman[296] introduced a most pertinent variation. He sensitized rabbits to horse serum and then prepared the skin by an intradermal injection of bacterial filtrate. Twenty-four hours later he gave horse serum intravenously, and within one hour the skin at the prepared site showed the typical necrotic reaction. He also demonstrated that other antigen-antibody reactions can produce the local skin lesions at a prepared site. Gerber[96] sensitized rabbits with 1 c.c. of horse serum per kilogram intravenously, followed six days later by an intravenous injection of bacterial filtrate. Six or twenty-four hours later he repeated the intravenous injection of horse serum and produced scattered vascular lesions, with especially marked degenerative changes in the heart. Controls receiving only the two injections of horse serum six days apart showed no vascular involvement.

To recapitulate, then, necrotizing arteritis in man has been preceded or accompanied by bronchial asthma, a variety of allergic states, acute and chronic bacterial infections, protozoan infestation, drug administration, and serum sickness. Experimentally, lesions of this type have been produced by an even greater variety of agents and methods: bacteria, bacterial products, foreign serum, serum plus sulfonamide drugs, isoantibodies alone and with bacteria, nephrotoxic sera, and experimental hypertension by various methods most of which depend on renal damage and renal tissue necrosis with or without infection.

Since in only one or two of these situations is it possible to show qualitative and quantitative similarities to the Arthus experiment, it follows that the vascular necrosis does not always represent an Arthus reaction, but rather it is more often an expression of other types of allergic reactions. The clinical and experimental observations which have been reviewed suggest that the mechanism illustrated by the Sanarelli-Shwartzman reaction may be one of the basic ones. We must assume in this case that a variety of agents can act as the "preparatory" stimulus which produces sensitivity (if not sensitization) of the blood vessels. The "provocative" agent, although it may react specifically with corresponding antibody, may then be considered to be nonspecific in initiating a violent vascular reaction.

The nature of the agents which can act as vascular sensitizers must be quite varied. There is a strong possibility that in any hypersensitive state the reactivity of blood vessels is so altered that they are capable of a severe reaction to what would otherwise be a negligible stimulus, as evidenced by the almost constant vascular component in all allergic manifestations. The frequent occurrence of bacterial infections preceding the onset of visceral angiitis suggests that the vascular reaction can occur either as a result of "preparation" of the blood vessels by bacteria or their products followed by a second precipitating reaction, or that the bacterial reaction may act as the "provocative" agent on vessels previously sensitized either to the same or to other bacteria, or to other even less related agents. The extremely severe exacerbation in the course of an acute lupus erythematosus which is often seen if one attempts to eradicate a focus of infection may thus be considered a true Sanarelli-Shwartzman phenomenon due to the sudden liberation of bacteria and/or bacterial products. This suggested explanation is compatible with the severe clinical picture and with the experimental data. In the subacute or chronic phase, on the other hand, tampering with foci of infection is less dangerous because of the decreased state of sensitivity. It would seem that the milder reactions must be due to a difference in the host, for it has been shown that a surgical procedure such as tonsillectomy or tooth extraction results in a high number of cases in the entrance of bacteria into the blood stream. Some are reluctant to concede that the foci of infection are important in lupus erythematosus because of the failure of chemotherapy or antibiotic therapy to alter the course. But if our concept is correct, this is exactly as expected, for even if all the organisms should be killed, this would not affect the established sensitivity of the blood vessels. Bacteria and other substances may act either as the sensitizing or provocative agent, and in the latter case the dosage would certainly determine the severity of the reaction.

A plausible explanation can also be advanced for the way in which severe reactions occur following the administration of a drug to which no previous exposure can be demonstrated. Landsteiner's studies[185,190] have shown that sensitization to simple chemical compounds and transfer of cutaneous sensitivity is possible. The studies of Schönholzer,[284] Davis,[65] and Wedum[327] have shown that the sulfonamides become antigenic by being bound to plasma protein. Nevertheless this antigenicity must operate in two ways. In cases of previous exposure to the drug a specific sensitization to drug-protein conjugate exists, but the immediate reaction to what appears to be the first contact with the antigen cannot be of this type (since it is immediate) and fits into the nonspecific reaction we have postulated. In reactions which develop more slowly, it is impossible of course to dismiss the possibility that a sufficient amount of circulating antigen remains to produce a specific reaction, yet everything points to the probability that foreign substances are fairly quickly removed from the blood stream.

The possibility that endogenous products of metabolism may be able to act as vascular sensitizers or as necrotizing factors has some support. Endocrine secretions may be considered as an example of products of normal metabolism. The administration of estrogenic substances seldom produces toxicity, but in some cases[201,326] purpura is produced. Watson et al[326] demonstrated skin sensitivity to estrogens in three of the five cases of purpura, and negative Prausnitz-Küster transfer reactions indicated an absence of circulating antibody. Purpura has been associated with menstruation,[64,75,79,222,229,297] puberty[101,194] and pregnancy.[279] The subject of sensitivity to endogenous hormones has been adequately covered by Zondek,[345] and no more need be said here.

A second possible source of endogenous sensitizers or necrotizers is tissue breakdown as a result of pathological conditions, or even from normal catabolism.[313] Loomis[203] has shown that renal infarction in rats produces hypertension and disseminated necrotizing arteritis. Since partial infarction of one kidney produced

hypertension whereas infarction of the entire kidney gave equivocal results, it seems probable that some of the effects depend on absorption of products of necrotic renal tissue into the blood stream. Damage of renal tissue is common to most of the studies on experimental hypertension and necrotizing arteritis so that the possibility that vasopressor and necrotizing substances are produced cannot be ruled out. Lesions characterized by vascular necrosis have been produced by injection of pig "rennin"[193] and also by methods which apparently exclude the participation of necrotic renal tissue, such as bilateral nephrectomy,[134,336] indicating that if products of necrotic tissue are responsible they are not necessarily derived only from kidney tissue. It is difficult to accept the involved logic necessary to explain hypertension as due to renal factors alone when removal of the damaged kidney does not produce a drop in the blood pressure, or when it can be produced by removing both kidneys. Nevertheless, it is admitted that renal damage is probably the most powerful producer of hypertension known. It is interesting to recall the previously quoted[9] high incidence of renal involvement in periarteritis nodosa (88 per cent) which is lower than the reported incidence of hypertension in this disease. As far as the specific vascular reaction is concerned, the possibility that blood vessels are sensitized by their own breakdown products cannot be dismissed. Equally intriguing is the speculation that a certain degree of organ specificity on the basis of organ autoantibodies would explain the organ-localization of the vascular reaction. Some support for this can be derived from the studies of Cavelti.

There is evidence that products of necrotic tissue do not always act independently. Smith et al[298] demonstrated the importance of coexisting perirenal infection in the production of hypertension and necrotizing arteritis in rats by the silk perinephritis method. Cavelti[54] showed that whereas injection of rabbit kidney tissue in rabbits did not result in the production of demonstrable antibodies, the addition of killed bacteria or bacterial filtrates to the injected kidney tissue gave rise to high titers. Freund[89] demonstrated that killed tubercle bacilli acted as "adjuvants" for the antigenicity of injected foreign substances, while Landsteiner[187] included "nonspecific factors" into the scheme of production of sensitivity to simple chemical compounds.

It would be reasonable to consider "adjuvants" as mere intensifiers of antigenic activity were it not for Shwartzman's demonstration[296] that if he sensitized rabbits to horse serum and then prepared the skin by an intradermal injection of bacterial filtrate, an intravenous injection of horse serum produced within one hour a typical necrotic skin reaction at the prepared site Gerber[96] produced widespread vascular necrosis by a modification of this experiment. He sensitized rabbits with horse serum intravenously, and six days later he followed this with an intravenous injection of a bacterial filtrate. Six to twenty-four hours later he repeated the administration of horse serum and found that scattered vascular necrosis resulted. Control animals receiving only two injections of horse serum six days apart showed no vascular lesions. Equally significant is the production of widespread vascular necrosis in pregnant rabbits by a single intravenous administration of bacterial filtrate, whereas in nonpregnant rabbits lesions are not produced unless the first injection is followed by a second. It seems plausible to suggest that some product of pregnancy acts as the preparatory substance so that a single injection of bacterial filtrate can act provocatively.

These highly significant experiments have attracted too little notice. They suggest that blood vessels may be so altered in their reactivity by a given substance that a totally unrelated material or antigen-antibody reaction which alone is too weak to produce demonstrable lesions is able to produce vascular necrosis. How this sensitization and nonspecific reaction takes place remains to be worked out. It should prove to be of fundamental importance in understanding the role

of altered vascular reactivity in the production of disease. For example, the recent re-emphasizing of the possible role of infection and bacterial invasion into blood vessels in arteriosclerosis[155] suggests that further studies may justify the inclusion into this basic vascular mechanism of a condition which has long been considered a "degenerative" disease accompanying old age.

The evidence to date does not allow a conclusion as to which of several mechanisms of sensitization is most important for the production of vascular lesions. The Arthus type, so effective in animals, may also be a factor in humans, although the large amounts of antigen necessary suggest that other types are more often involved. It is likely that the Sanarelli-Shwartzman type is one of the chief reactions, but certainly not the only one. Indeed, the mechanisms of vascular allergy are probably as numerous and as varied as the characteristic allergic phenomena. We look forward to new developments in this field.

REFERENCES

1. Abell, R. G., and Scheuck, H. P.: Microscopic observations of the behavior of living blood vessels of the rabbit during the reaction of anaphylaxis. J. Immunol., 34:195, 1938.
2. Agduhr, E.: Post natal development under different conditions of nutrition and circumstances of functioning; changes in heart. through presence of cod liver oil (oleum jecoris Aselli) in food. Acta Paediat., 5:319, 1926.
3. Agduhr, E.: Cod liver oil in therapeutic doses causes organic changes. Am. J. Physiol., 90:260, 1929.
4. Aikawa, J. K.: Hypersensitivity and rheumatic fever. Ann. Int. Med., 23:983, 1945.
5. Alexander, H. L., and Eyermann, C. H.: Allergic purpura. J.A.M.A., 92:2092, 1929.
6. Anderson, T.: Arteritis temporalis (Horton) (symptom of generalized vascular disease): survey and case with glaucoma. Acta med. Scandinav., 128:151, 1947.
7. Apitz, K.: Die Wirkung bakterieller Kulturfiltrate nach Unstimmung des gesmanten Endothels beim Kaninchen. Virchow's Arch. f. path. Anat., 293:1, 1934.
8. Apitz, K.: Study of generalized Shwartzman phenomenon. J. Immunol., 29:255, 1935.
9. Arkin, A.: Clinical and pathological study of periarteritis nodosa; report of five cases, one histologically healed. Am. J. Path., 6:401, 1930.
10. Aronson, J. D.: Tissue culture studies on the relation of the tuberculin reaction to anaphylaxis and the Arthus phenomena. 25:1, 1933.
11. Aronson, J. D.: The specific cytotoxic action of tuberculin in tissue culture. J. Exper. Med., 54:387, 1931.
12. Aronson, J. D., and Nicholas, R. V.: The comparative value of tuberculoprotein (MA-100) and old tuberculin, with special reference to sensitization. J. Immunol., 25:483, 1933.
13. Arthus, M.: Injections répétées de sérum du cheval chez le lapin. C. R. Soc. Biol., 55:817, 1903.
14. Arthus, M., and Breton, M.: Lesions cutanées produites par les injections de sérum de cheval chez le lapin anaphylactisé par et pour ce sérum. C. R. Soc. Biol., 55:1478, 1903.
15. Aschoff, L.: Pathologische Anatomie. Jena: Gustav Fischer, 1921.
16. Aschoff, L.: Zur [illegible] d. deutch. path. Gesellschft., 8:46, 1904.
17. Askanazy, M.: D[illegible] bei der akuten tuberkulösen Meningitis und ihre beziehungen zu [illegible] Deutsches Arc. f. klin. Med., 99:333, 1910.
18. Baehr, G.; Klemp[illegible] A.: Diffuse disease of peripheral circulation usually associated with lupus erythematosus and endocarditis. Tr. A. Am. Physicians, 50:262, 1936.
19. Bagenstoss, A. E., Bayley, E. C., and Lindberg, D. O. N.: Löffler's syndrome. Report of a case with pathologic examination of the lungs. Proc. Staff Meet., Mayo Clin., 21:457, 1946.
20. Bain, C. W. C.: Arteritis of the temporal arteries. Lancet, 1:424, 1938.
21. Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, the Libman-Sacks syndrome, and polyarteritis nodosa? New England J. Med., 225:433, 1941.
22. Barker, N. W., and Baker, T. W.: Proliferative initimitis of small arteries and veins associated with peripheral neuritis, livedo reticularis, and recurring necrotic ulcers of the skin. Ann. Int. Med., 9:1134, 1936.
23. Barker, N. W., and Brown, G. E.: Progressive disseminated obliterating arteritis of unknown origin. M. Clin. North America, 16:1313, 1933.
24. Basinski, D. H., and Hummel, J. P.: Further observations on succinic dehydrogenase system and effects of tocopherol esters. J. Biol. Chem., 167:339, 1947.
25. Benda, C.: Die Gefässe. Aschoff's Pathologische Anatomie. Jena: Gustav Fischer, Bd. II, S. 74, 1921.
26. Bennett, G. A., and Levine, S. A.: Two cases of periarteritis nodosa, one with unusual manifestations (meningeal form). Am. J. M. Sc., 177:853, 1929.
27. Berger, H. C.: Eosinophilia occurring in chorea. Am. J. Dis. Child., 21:477, 1921.
28. Bergstrand, H.: Morphologic equivalents in polyarthritis rheumatica, periarteritis nodosa, transient eosinophilic infiltration of lung, and other allergic syndromes. J. Path. & Bact., 58:399, 1946.
29. Bevans, M.: Pathology of scleroderma, with special reference to changes in gastrointestinal tract. Am. J. Path., 21:25, 1945.
30. Bing, J.: Further investigations on hyperglobulinemia (Is serum-globulin formed from plasma cells and reticuloendothelial cells?) Acta. med. Scandinav., 103:565, 1940.
31. Bing, J.: Further investigations on hyperglobulinemia (Occurrence and degree of hyperglobulinemia in various diseases. Ratio between hyperglobulinemia, hyperproteinemia, and hypoalbuminemia. Formol-gel reaction). Acta med. Scandinav., 103:547, 1940.

32. Bjorneboe, M., and Gormsen, H.: Preliminary report on investigations on occurrence of plasma cells in experimental hyperglobulinemia in rabbits. Nord. med. (Hospitalstid), 9:891, 1941.
33. Bjorneboe, M., and Gor [illegible] las Vorkommen von Plasmazellen bei experimenteller [illegible] (Vorläufige Mitteilung). Klin. Wchnschr., 20:314, 1941.
34. Bjorneboe, M., and Gormsen, H.: Experimental studies on the role of plasma cells as antibody producers. Acta Path. et microbiol. Scandinav., 20:649, 1943.
35. Black-Schaffer, B.: Pathology of anaphylaxis due to sulfonamide drugs. Arch. Path., 39:301, 1945.
36. Black-Schaffer, B.; Hiebert, T. G., and Kerby, G. P.: Experimental study of purpuric meningococcemia in relation to the Shwartzman phenomenon. Arch. Path., 43:28, 1947.
37. Boas, E. P.: Some immediate causes of cardiac infarction. Am. Heart J., 23:1, 1942.
38. Bohrod, M. G.: Periarteritis nodosa-like lesions in tuberculous meningitis. New York State J. Med., 48:275, 1948.
39. Brieger, H.: Über die allergische Natur des durch S. Thiazol erzeugten Erythema nodosum. Arch. Kinderh., 133:161, 1947.
40. Bronfenbrenner, J.: Hypersensitivity and immunity in the light of the "unitarian" hypothesis. J. Allergy, 19:71, 1948.
41. Brown, C. E., and Crane, G. L.: Bilateral cortical necrosis of the kidney following severe burns. J.A.M.A., 122:871, 1943.
42. Bruun, E.: Experimental investigation in serum allergy. London: Oxford University Press, 1940.
43. Bunim, J. J.: Lupus erythematosus disseminatus. Ann. Int. Med., 13:1399, 1940.
44. Burgess, J. F.: Vitamin E (tocopherols) in the collagenoses. Lancet, 255:215, 1948.
45. Cannon, P. R.; Walsh, T. E., and Marshall, C. E.: Acute local anaphylactic inflammation of lungs. Am. J. Path., 17:777, 1941.
46. Cannon, P. R., and Marshall, C. E.: An improved serological method for the determination of precipitated titers of antisera. J. Immunol., 38:365, 1940.
47. Cannon, P. R., and Marshall, C. E.: Studies on the mechanism of the Arthus phenomenon. J. Immunol., 29:29, 1935.
48. Carter, H. F., and D'Ambrera, V. St. E.: Mites (acarina) probable factor in etiology of spasmodic bronchitis and asthma associated with high eosinophilia. Tr. Roy. Soc. Trop. Med. & Hyg., 39:373, 1946.
49. Castberg, T., and Schwartz, M.: Changes in electrocardiogram during allergic shock. Acta med. Scandinav., 126: 459, 1947.
50. Cavelti, A. P.: Studies on the pathogenesis of rheumatic fever. II. Cardiac lesions produced in rats by means of autoantibodies to heart and connective tissue. Arch. Path., 44:13, 1947.
51. Cavelti, A. P.: Pathogenesis of glomerulonephritis and rheumatic fever. In vivo activation of tissue antigens as a result of streptococcal infection and consecutive formation of autoantibodies. Arch. Path., 44:119, 1947.
52. Cavelti, P. A.: Studies on the technic of collodion agglutination. Influence of certain qualities of the collodion particles and of the proportions of antigen and collodion on the sensitivity and specificity of the reaction. J. Immunol., 49:365, 1944.
53. Cavelti, P. A.: Studies on the pathogenesis of rheumatic fever. I. Experimental production of autoantibodies to heart, skeletal muscles, and connective tissue. Arch. Path., 44:1, 1947.
54. Cavelti, P. A., and Cavelti, E. S.: Studies on the pathogenesis of glomerulonephritis; production of autoantibodies to kidney in experimental animals. Arch. Path., 39:148, 1945.
55. Cavelti, P. A., and Cavelti, E. S.: Studies on pathogenesis of glomerulonephritis; production of glomerulonephritis in rats by means of autoantibodies to kidney. Arch. Path., 40:158, 1945.
56. Cavelti, P. A., and Cavelti, E. S.: Studies on pathogenesis of glomerulonephritis; clinical and pathologic aspects of experimental glomerulonephritis produced in rats by means of autoantibodies to kidney. Arch. Path., 40:163, 1945.
57. Chase, M. W.: The cellular transfer of cutaneous hypersensitivity to tuberculin. Proc. Soc. Exper. Biol. & Med., 59:134, 1945.
58. Christian, H. A.: Long-continued fever with inflammatory changes in serous and synovial membranes and eventual glomerulonephritis: A clinical syndrome of unknown etiology. M. Clin. North America, 18:1023, 1935.
59. Clark, E., and Kaplan, B. I.: Endocardial, arterial, and other mesenchymal alterations associated with serum disease in man. Arch. Path., 24:458. (Oct.) 1937.
60. Coburn, A. F.: The Factor of Infection in the Rheumatic State. Baltimore: Williams and Wilkins Co., 1931.
61. Coburn, A. F., and Moore, D. H.: Plasma proteins in disseminated lupus erythematosus. Bull. Johns Hopkins Hosp., 73:196, 1943.
62. Cole, J., and Korns, H. M.: Visceral manifestations of angio-neurotic edema; report of a case with recurrent pulmonary involvement. J. Allergy, 5:347, 1933.
63. Culbertson, J. R.: Relationship of circulating antibody to the Arthus Phenomenon. J. Immunol., 29:29, 1935.
64. David, W.: Über 'Purpura'—Erkrankungen bei Frauen. Med. Klin., 22:1755, 1926.
65. Davis, B. D.: Binding of sulfonamides by plasma proteins. Science, 95:78, 1942.
66. deLavergne, V., Morel and Jocham: Syndrome de Stokes-Adams transitoire, surveure en même temps que des accidents sériques. Bull. et. Soc. med. des Hôsp. de Paris, 51:1314, 1927.
67. DeMuro, P., and Ficari, A.: Experimental studies on allergic cholecystitis. Gastroenterology, 6:302, 1946.
68. Denzer, B. S., and Blumenthal, S.: Acute lupus erythematosus disseminatus. Am. J. Dis. Child., 53:525, 1937.
69. Doan, C. A.; Sabin, F. R., and Forkner, C. E.: Reaction of the connective tissues of the normal rabbit to water soluble protein and polysaccharide. J. Exper. Med., 52:(suppl. 3) 73, 1930.
70. Dowling, G. B.: Dermatomyositis. St. Thomas Hosp. Rep., 1:150, 1936.
71. Duff, G. L., and Murray, E. G. D.: Bilateral cortical necrosis of the kidneys. Am. J. M. Sc., 201:428, 1941.
72. Duke, W. W.: Relationship of heat and effort sensitiveness and cold sensitiveness to functional cardiac disorders including angina pectoris, tachycardia and ventricular extrasystoles. J. Allergy, 4:38, 1932.

73. Eason, J., and Carpenter, G.: Treatment of acute rheumatic polyarthritis with concentrated anti-scarlatinal serum. Quart. J. Med., 30:93, 1937.
74. Eiman, J., and Gouley, B. A.: Rheumatic pneumonitis. Arch. Path., 5:558, 1928.
75. Ellman P., and Weber, F. P.: Recurrent menstrual purpura and vicarious menstruation. Brit. J. Dermat., 47:197, 1935.
76. Epstein, E. Z., and Greenspan, E. B.: Rheumatic pneumonia. Arch. Int. Med., 68:1074, 1941.
77. Epstein, S.: Eczema—allergic dermatitis; review of recent literature. Ann. Allergy, 2:247, 1944.
78. Epstein, S.: Physical allergy in dermatology. A review of recent literature. Ann. Allergy, (to be published).
79. Evans, H., and Perry, K. M. A.: Thrombocytopenic purpura. Lancet, 2:410, 1943.
80. Fahr, T.: Zur Frage der Polymyositis (Dermatomyositis). Arch. f. Dermat. u. Syph., 130:1, 1921.
81. Fischell, E. E., and Kabat, E. A.: Quantitative study of the Arthus phenomenon induced passively in the rabbit. J. Immunol., 55:337, 1947.
82. Fleischhacker, H.: Über die Bedeutung der Reticuloendothelien und Plasmazellen des Knochenmarkes. Ergebn. d. inn. Med. u. Kinderh., 60:508, 1941.
83. Fleischhacker, H.: Über die Plasmazellen und das reticuloendotheliale System des Knochenmarkes; Beitrag zur Herkunft der Plasmaeiweisskörper. Deutsches Arch. f. klin. Med., 186:506, 1940.
84. Fleisher, M. S., and Jones, L.: Serum sickness in rabbits. J. Exper. Med., 54:597, 1931.
85. Fox, R. A.: Disseminated lupus erythematosus—allergic disease? Arch. Path., 36:311, 1943.
86. Fox, T. T., and Messeloff, C. R.: [illegible] nges in a case of serum sickness due to tetanus toxoid. New Yor[illegible] . 1942.
87. French, A. J.: Hypersensitivity in [illegible] histopathologic changes associated with sulfonamide chemotherapy. [illegible] . 1946.
88. French, A. J., and Weller, C. V.: Interstitial myocarditis following clinical and experimental use of sulfonamide drugs. Am. J. Path., 18:109, 1942.
89. Freund, J., and McDermott, K.: Sensitization to horse serum by means of adjuvants. Proc. Soc. Exper. Biol. & Med., 49:548, 1942.
90. Friedberg, C. K., and Gross, L.: Nonbacterial thrombotic endocarditis associated with acute thrombocytopenic purpura. Arch. Int. Med., 58:641, 1936.
91. Friedberg, C. K., and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease. Arch. Int. Med., 54:170, 1934.
92. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions. Arch. Int. Med., 58:662, 1936.
93. Friedman, B.; Jarman, J., and Klemperer, P.: Sustained hypertension following experimental unilateral renal injuries. Effect of nephrectomy. Am. J. M. Sc., 202:20, 1941.
94. Furth, J.: Antigenic character of heated protein. J. Immunol., 10:777, 1925.
95. Geipel: Myokarditis. Munch. med. Wchnschr., 54:1057, 1907.
96. Gerber, I. E.: The Shwartzman phenomenon in the kidneys of rabbits. Observations on effects of intravenous administration of bacterial filtrates. Arch. Path., 21:776, 1936.
97. Gerlach, W.: Studien über hyperergische Entzundung. Virch. Arch., 247:294, 1923.
98. Gilman, R. L.: The Senear-Usher syndrome; dermatosis combining features of lupus erythematosus. Arch. Dermat. & Syph., 13:761, 1926.
99. Ginzler, A. M., and Fox, T. T.: Disseminated lupus erythematosus; cutaneous manifestation of systemic disease (Libman-Sacks); report of case. Arch. Int. Med., 65:26, 1940.
100. Goeckerman, W. H.: Lupus erythematosus as systemic disease. J.A.M.A., 80:542, 1923.
101. Goldburgh, A. L., and Gouley, B. A.: Postpubertal menorrhagia and its possible relations to thrombocytopenic purpura hemorrhagica. Am. J. M. Sc., 200:499, 1940.
102. Goldzieher, J. W., and Lisa, J. R.: Gross cerebral hemorrhage and vascular lesions in acute tuberculous meningitis and meningo-encephalitis. Am. J. Path., 23:133, 1947.
103. Goodman, Morton, J.: Periarteritis nodosa with recovery: Report of an unusual case apparently due to sensitivity to sulfadiazine. Ann. Int. Med., 28:181, 1948.
104. Gormsen, H., and Heintzelmann, F.: Behavior of sedimentation reaction, serum proteins, and sternal punctate in serum sickness. Nord. med. (Hospitalstid.), 11:2125, 1941.
105. Gouley, B. A.: The evolution of the parenchymal lung lesion in rheumatic fever. Am. J. M. Sc., 196:1, 1938.
106. Gouley, B. A., and Eiman, J.: The pathology of rheumatic pneumonitis. Am. J. M. Sc., 183:359, 1932.
107. Govier, W. M.; Bergman, V., and Beyer, K. H.: Studies on mechanism of action of sympathomimetic amines; effect of sympathomimetic amines on succinoxidase system as influenced by presence of a-tocopherol phosphate. J. Pharmacol., 85:143, 1945.
108. Gratia, A., and Linz, R.: Les phénoménes de Sanarelli et de Shwartzman ou l'allergie hemorragique. Ann. Inst. Pasteur, 49:131, 1932.
109. Gregory, J. E., and Rich, A. R.: The experimental production of anaphylactic pulmonary lesions with the basic characteristics of rheumatic pneumonitis. Bull. Johns Hopkins Hosp., 78:1, 1946.
110. Griffiths, J. J.: Demonstration of agglutination and an agglutinin 'blocking' property in sera of known cases of brucellosis. J. Bact., 54:269, 1947.
111. Gross, L.: The heart in atypical verrucous endocarditis (Libman-Sacks). Libman Anniv. Vols., 2:527, 1932.
112. Gross, L.: Cardiac lesions in Libman-Sacks disease with consideration of its relationship to acute diffuse lupus erythematosus. Am. J. Path., 16:375, 1940.
113. Gross, L.; Loewe, L., and Eliasoph, B.: Attempt to produce rheumatic fever in animals. J. Exp. Med., 50:41, 1929.
114. Gruber, G. B.: Zur Frage der Periarteritis nodosa, mit besonderer Berüchsichtigung der Gallenblasen—und Nieren Beteiligung. Virchow's Arch. f. Path. Anat., 258:441, 1923.
115. Gullickson, T. W., and Calverley, C. E.: Cardiac failure in cattle on vitamin-E free rations as revealed by electrocardiograms. Science, 104:312, 1946.
116. Hagebush, O. E.; Robben, F. J.; Fleisher, M. S., and Jones, L.: Serum sickness in rabbits. Reactions of body temperature and leucocytic curves. J. Immunol., 22:373, 1932.
117. Haining, R. B., and Kimball, T. S.: Polyarteritis nodosa. Am. J. Path., 10:349, 1934.
118. Ham, A. W.: Coronary and aortic sclerosis, periarteritis nodosa, chronic nephritis and hypertension as sequelae to a single experimentally produced widespread calcium precipitation in the rat. Arch. Path., 29:731, 1940.
119. Hansen-Pruss, O. C., and Goodman, E. G.: Allergic pulmonary consolidations (Löffler syndrome). Ann. Allergy, 2:85, 1944.

120. Harkavy, J.: Vascular allergy; pathogenesis of bronchial asthma with recurrent pulmonary infiltration and eosinophilic polyserositis. Arch. Int. Med., 67:709, 1941.
121. Harkavy, J.: Vascular allergy. J. Allergy, 14:507, 1943.
122. Harkavy, J.: Vascular allergy. Clinics, 5:504, 1946.
123. Harkavy, J.: Cardiac arrhythmia with special reference to paroxysmal tachycardia, auricular fibrillation and premature beat in constitutionally allergic individuals. J. Mt. Sinai Hosp., 5:273, 1938.
124. Harris, W. H.: Etiology and pathology of periarteritis nodosa. South. Med. J., 19:344, 1926.
125. Hartley, P.: The role of ether-soluble constituents of serum in certain serological reactions. Brit. J. Exper. Path., 6:189, 1925.
125a Hehre, E., and Freund, J.: Sensitization, antibody formation and lesions produced by tubercle bacilli in the albino rat. Arch. Path., 27:289, 1939.
126. Heidelberger, M., and Anderson, D. G.: Immune response of human beings to brief infections with pneumococcus. J. Clin. [illegible] 1944.
127. Heidelberger, M., and MacPherson, C [illegible] micro-estimation of antibodies in sera of man and other animals. S [illegible]
128. Heidelberger, M., and MacPherson, C. F. C[illegible]: Correction to reference above (Science, 97: 405, 1943). Science, 98:63, 1943.
129. Henning, L.: Gelingt es bei Meerschweinchen mit Gemischen aus alkoholischen Extrakten arteigener Organe und Schweineserum positive Seroreaktionen, sowie anaphylaktische Lipoid-Antikörper zu erzeugen? Ztschr. f. Immunitätsforsch u. exper. Therap., 55:19, 1928.
130. Herbut, P. A., and Kinsey, F. R.: Transitory pulmonary infiltrations (Löffler's syndrome) in rabbits. Arch. Path., 41:489, 1946.
131. Hickman, K. C. D., and Harris, P. L.: Advances in Enzymology. 6:469, 1946.
132. Holly, S. W.: Corneal reactions of normal and of tuberculous guinea pigs to tuberculo-protein and tuberculo-phosphatide. Am. J. Path., 11:937, 1935.
133. Holman, R. L.: Acute necrotizing arteritis, aortitis, and auriculitis, following uranium nitrate injury in dogs with altered plasma proteins. Am. J. Path., 17:359, 1941.
134. Holman, R. L.: Experimental necrotizing arteritis in dogs. III. Bilateral nephrectomy as effective as heavy metal injury in its production. Am. J. Path., 19:147, 1943.
135. Holman, R. L.: Experimental necrotizing arteritis in dogs. IV. Alteration of the blood plasma proteins not essential. Am. J. Path., 19:159, 1943.
136. Holman, R. L.: Necrotizing arteritis in dogs related to diet and renal insufficiency. V. Evidence for a dietary factor. Am J. Path., 14:977, 1943.
137. Holman, R. L.: Necrotizing arteritis in dogs related to diet and renal insufficiency. VI. Associated lesions: stomatitis, gastroenteritis, and pancreatic fat necrosis. Am. J. Path., 19:993, 1943.
138. Holman, R. L.: Prevention of experimental arteritis in dogs by Vitamin E. Proc. Soc. Exper. Biol. & Med., 66:307, 1947.
139. Holman, R. L., and Hewitt, W. C.: Experimental necrotizing arteritis. II. Mercuric chloride as effective as uranium nitrate in its production. Proc. Soc. Exper. Biol. & Med., 49:58, 1942.
140. Holman, R. L., and Swanton, M. C.: 'Dietary factor' in necrotizing arteritis in dogs a lipid substance. Proc. Soc. Exper. Biol. & Med., 63:87, 1946.
141. Horsfall, F. L., Jr., and Goodner, K.: Lipoids and immunological reactions; the relation of phospholipids to type-specific reactions of anti-pneumococcus horse and rabbit sera. J. Exper. Med., 62:485, 1935.
142. Horsfall, F. L., Jr., and Goodner, K.: Lipids and immunological reactions; further experiments on relation of lipids to type-specific reactions of anti-pneumococcus sera. J. Immunol., 31:135, 1936.
143. Horton, B. T., and Magath, T. B.: Arteritis of the temporal vessels: Report of seven cases. Proc. Staff Meet., Mayo Clin., 12:548, 1937.
144. Horton, B. T.; Magath, T. B., and Brown, G. E.: An undescribed form of arteritis of the temporal vessels. Proc. Staff Meet., Mayo Clin., 7:700, 1932.
145. Horton, B. T.; Magath, T. B., and Brown, G. E.: Arteritis of the temporal vessels; previously undescribed form. Arch. Int. Med., 53:400, 1934.
146. Houchin, O. B.: In vitro effect of a-tocopherol and its phosphate derivative on oxidation in muscle tissue. J. Biol. Chem., 146:313, 1942.
147. Houchin, O. B., and Matill, H. A.: Influence of parenteral administration of a-tocopherol phosphate on metabolic processes in dystrophic muscle. J. Biol. Chem., 146:309, 1942.
148. Hoyne, A. L., and Steiner, M. M.: Periarteritis nodosa complicating scarlet fever with unusual syndrome of nephritis and polyneuritis. Am. J. Dis. Child., 59:1271, 1940.
149. Huebschmann: Das Verhalten der Plasmazellen in der Milz bei infektiosen Prozessen. Verhandl. d. deutsch. Path. Gesellsch., 16 Tag, Marburg, pp. 110, 1913.
150. Humphreys, E. M.: The cardiac lesions of acute disseminated lupus erythematosus. Ann. Int. Med., 28:12, 1948.
151. Jadassohn, J.: Lupus erythematosus. in Mracek, F.: Handbuch der Hautkrankheiten. Vienna: Alfred Hoelder, 1904, Vol. 3.
152. Jaffe, R.: Las lesiones miocárdicas y hepáticas en animales alergicos. Rev. sudam. morfol., 4:107, 1946.
153. Jarcho, S.: Lupus erythematosus associated with visceral vascular lesions; series of autopsied cases. Bull. Johns Hopkins Hosp., 59:262, 1936.
154. Jennings, G. H.: Arteritis of temporal vessels. Lancet, 1:424, 1938.
155. Jones, N. W., and Rogers, A. L.: Chronic infection and arteriosclerosis. Some additional experimental data. Arch. Path., 45:271, 1948.
156. Jores, L.: Periarteritis nodosa. Henoke-Lubarsch Hdbch. d. spez. path. Anat. u. Histol., Berlin, 2:652, 1924.
157. Junghans, E.: Weiters Untersuchung uber die hyperergische Entzündung, insbesondere die Aortitis. Ziegler's Beitr., 55:467, 1934.
158. Kabat, E. A., and Boldt, M. H.: Quantitative study of passive anaphylaxis in the guinea pig, II. J. Immunol., 48:181, 1944.
159. Kabat, E. A., and Landow, H.: A Quantitative study of passive anaphylaxis in the guinea pig, I. J. Immunol., 44:69, 1942.
160. Kagan, B. M.: Hyperglobulinemia. Am. J. M. Sc., 206:309, 1943.
161. Kaposi, M.: Neue Beitrage zur Kenntnis des Lupus erythematodes. Arch. f. Dermat. u. Syph., 4:36, 1872.
162. Karsner, H. T., and Bayless, F.: Coronary arteries in rheumatic fever. Am. Heart J., 9:557, 1934.

163. Karsner, H. T.; Ecker, E. E., and Jackson, E. L.: Shwartzman phenomenon in rabbit stomach. Proc. Soc. Exper. Biol. & Med., 29:319, 1931.
164. Kaunitz, H., and Pappenheimer, A. M.: Oxygen consumption in vitamin E deficiency. Am. J. Physiol., 138:328, 1943.
165. Keefer, C. S., and Felty, A. R.: Acute disseminated lupus erythematosus. Report of three fatal cases. Bull. Johns Hopkins Hosp., 35:294, 1924.
166. Keil, H.: Relationship between lupus erythematosus and tuberculosis; critical review based on observations at necropsy. Arch. Dermat. & Syph., 28:765, 1933.
167. Keil, H.: Relatinn between "systemic" lupus erythematosus and a peculiar form of thrmnbocytopenic purpura. Brit. J. Dermat., 49:221, 1937.
168. Keil, H.: Dermatomyositis and systemic lupus erythematosus: I. A clinical report of "transitional" cases with a consideration of lead as a possible etiologic factor. Arch. Int. Med., 66:109, 1940.
169. Keil, H.: Conception of lupus erythematosus and its morphologic variants, with particular reference to "systemic" lupus erythematosus. Arch. Dermat. & Syph., 36:729, 1937.
170. Kimmelstiel, P.: Acute hematogenous interstitial nephritis. Am. J. Path., 14:737, 1938.
171. Kirchheimer, W. F., and Weiser, R. S.: Passive transfer of tuberculin sensitivity with cells of tuberculous guinea pigs. Proc. Soc. Exper. Biol. & Med., 66:166, 1947.
172. Kleczkowski, A.: The effect of heat on the flocculating antibodies of rabbit antisera. Brit. J. Exper. Path., 22:192, 1941.
173. Kleczkowski, A.: The conversinn of non-precipitating inhibiting protein complexes into forms again precipitable by antisera to the original proteins. Brit. J. Exper. Path., 26:33, 1945.
174. Kleczkowski, A.: Specific precipitation nf one protein by nne antiserum to another. Brit. J. Exper. Path., 26:41, 1945.
175. Klemperer, P.: The pathogenesis of lupus erythematosus and allied conditions. Ann. Int. Med., 28:1, 1948.
176. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosus. Arch. Path., 52:569, 1941.
177. Klinge, F.: Der Rheumatismus. Ergeb. d. allg. Path., 27:1, 1933.
178. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke. Experimentelle pathologisch-anatomische Studie zur Pathogenese des Gelenkrheumatismus. Beitr. z. path. Anat. u. z. allg. Path., 83:185, 1929.
179. Kolouch, F.: A study of the bnne marrow plasma cell of mammals with special reference to its nrigin in the rabbit under normal and experimental conditions. Thesis, University of Minnesota, 1, 1938.
180. Kolouch, F.: Origin of bone marrow plasma cell associated with allergic and immune states in rabbits. Proc. Soc. Exper. Biol. & Med., 39:147, 1938.
181. Kolouch, F.; Good, R. A., and Campbell, B.: The reticulo-endothelial origin of the bone marrow plasma cells in hypersensitive states. J. Lab. & Clin. Med., 32:749, 1947.
182. Krupp, M. A.: Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sacks "disease"): quantitative studies. Arch. Int. Med., 71:54, 1943.
183. Kussmaul, A., and Maier, R.: Über eine bisher nicht beschriebene eigenthümliche arterienenkrankung (Periarteritis Nodosa), die mit Morbus Brightii and rapid fortschritender allgemeiner Muskellahmung einhergehet. Deutsches Arch. f. klin. Med., 1:484, 1865.
184. Lamb, A. R.: Periarteritis nodosa—a clinical and pathological review of the disease. Arch. Int. Med., 14:481, 1914.
185. Landsteiner, K., and Chase, M. W.: Studies on sensitization nf animals with simple chemical compounds; anaphylaxis induced by picryl chloride and 2:4 dinitrochlorobenzene. J. Exper. Med., 66:337, 1937.
186. Landsteiner, K., and Chase, M. W.: Studies on sensitization of animals with simple chemical compounds; experiments on sensitization of guinea pigs to poison ivy. J. Exper. Med., 69:767, 1939.
187. Landsteiner, K., and Chase, M. W.: Studies on sensitization of animals with simple chemical compounds; skin sensitization induced by injection of conjugate. J. Exper. Med., 73:431, 1941.
188. Landsteiner, K., and Chase, M. W.: Experiments on transfer of cutaneous sensitivity to simple compounds. Proc. Soc. Exper. Biol. & Med., 49:688, 1942.
189. Landsteiner, K., and Jacobs, J.: Studies nn the sensitization of animals with simple chemical compounds. J. Exper. Med., 64:625, 1936.
190. Landsteiner, K., and Van der Scheer, J.: Anaphylactic shock by azo dyes. J. Exper. Med., 57:633, 1933.
191. Lebowich, J., and Hunt, H. D.: The diagnostic significance of eosinophilia in periarteritis nodosa. Am. J. Clin. Path., 10:642, 1940.
192. Lederer, M., and Rosenblatt, P.: Death during sulfathiazole therapy; pathologic and clinical observations on four cases with autopsies. J.A.M.A., 119:8, 1942.
193. Leiter, L., and Eichelberger, L.: Studies on renin: the duration of the pressor effect of large doses in conscious normal and renally abnormal dogs. Observations on anesthetized and uremic dogs and the anaphylactic and pathological effects of pig renin. J. Clin. Investigation, 22:11, 1943.
194. Leschke, E., and Wittkower, E.: Der Werlhofsche Blutfleckenkrankheit (thrombopenische Pupura). Ein Beitrag zur Pathologie der Blutplattchen und capillaren und zur Pathogenese der hamorrhagischen Diathese. Ztschr. f. klin, Med., 102:649, 1926.
195. Levine, P.; Burnham, L.; Katzen, E. M., and Vogel, P.: The role of iso-immunization in the pathogenesis of erythroblastosis fetalis. Am. J. Obst. & Gynec., 42:925, 1941.
196. Lihman, E., and Sacks, B.: A hitherto undescribed form of valvular and mural endocarditis. Arch. Int. Med., 33:701, 1924.
197. Lichtenstein, L., and Fox, L. J.: Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole. Am. J. Path., 22:665, 1946.
198. Lin, H. A. C.: Is toxemia of pregnancy an allergic reaction? Am. J. Obst. & Gynec., 54:97, 1947.
199. Löffler, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie). Beitr. z. Klin. d. Tuberk., 79:368, 1932.
200. Löffler, W.: Die flüchtigen Lungeninfiltrate mit Eosinophilie. Schweiz. med. Wchnschr., 66:1069, 1936.
201. Loftis, E. L.: Purpura due to injection of estrogenic substances. Arch. Dermat. & Syph., 43:138, 1940.

202. Longcope, W. T.: The production of experimental nephritis by repeated proteid intoxication. J. Exper. Med., 18:678, 1913.
203. Loomis, D.: Hypertension and necrotizing arteritis in the rat following renal infarction. Arch. Path., 41:231, 1946.
204. Loveless, M. H.: Immunological studies of pollinosis; presence of two antibodies related to same pollen-antigen in serum of treated hay fever patients. J. Immunol., 38:25, 1940.
205. Loveless, M. H.: Immunological studies of pollinosis; passive sensitization of man through transfusion. J. Immunol., 41:15, 1941.
206. Loveless, M. H.: Immunological studies of pollinosis; fluctuations in antibody titer of normal individuals subcutaneously and intravenously injected with pollen-extract over protracted periods. J. Immunol., 44:1, 1942.
207. Loveless, M. H.: Immunological studies of pollinosis; relationship between thermostable antibody in circulation and clinical immunity. J. Immunol., 47:165, 1943.
208. Ludy, J. B., and Corson, E. F.: Lupus erythematosus: increased incidence, hematoporphyrinuria, and spectroscopic findings. Arch. Dermat. & Syph., 37:403, 1938.
209. MacDonald, J. A., and Moser, R. H.: Periarteritis and arteritis of the temporal vessels; case report. Ann. Int. Med., 10:1721, 1937.
210. Markoff, N. G.: Die Reticuloendothelien des Knockenmarks, beurteilt durch Sternalpunktion. Deutsches Arch. f. klin. Med., 180:530, 1937.
211. Masugi, M., and Isibasi, T.: Über abergische Vorgänge bei Allgemeininfection von Standpunkt der experimentellen Forschung. Beitr. z. path. Anat. u. z. allg. Path., 96:391, 1936.
212. Masugi, M., and Sato, Y.: Über die allergische Gewebsreaktion der Niere. Zugleich ein experimenteller Beitrag zur Pathogenese der diffusen Glomerulonephritis und der Periarteritis nodosa. Virchow's Arch. f. Path. Anat., 293:615, 1934.
213. Masugi, M., and Yã, S.: Die diffuse Sklerodermie und ihre Gefässveranderung. Virchow's Arch. f. Path. Anat., 302:39, 1938.
214. McEwen, E. L.: Erythema multiforme: Report of case with necropsy findings and deductions. Arch. Dermat. & Syph., 13:331, 1926.
215. Merkel, W. C., and Crawford, R. C.: Pathologic lesions produced by sulfathiazole. J.A.M.A., 119:770, 1942.
216. Metz, W.: Die geweblichen Reaktionserscheinungen an der Gefässwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteritis nodosa. Beitr. z. path. Anat. u. z. all. Anat., 88:17, 1932.
217. Miale, J. B.: The hematologic response in dogs to the administration of anti-spleen serum. Blood, 2:175, 1947.
218. Miale, J. B.: Characteristic urinary findings in visceral angiitis (periarteritis nodosa, lupus erythematosus). Am. J. Clin. Path., 17:820, 1947.
219. Miale, J. B.; Doege, K. H., and Piehl, M.: Acute panarteritis in allergic persons. Arch. Int. Med., 80:791, 1947.
220. Middleton, W. S., and McCarter, J. C.: The diagnosis of periarteritis nodosa. Am. J. M. Sc., 190:291, 1935.
221. Miller, F. R.: Induced development and histogenesis of plasma cells. J. Exper. Med., 54:333, 1931.
222. Minot, G. R.: Purpura hemorrhagica with lymphocytosis; an acute type and an intermittent menstrual type. Am. J. M. Sc., 192:445, 1936.
223. Miura, T.: Untersuchungen über die experimentelle Serumkrankheit. Trans. Soc. Path. Jap., 30:378, 1940.
224. Moen, J. K., and Swift, H. F.: Tissue culture studies on bacterial hypersensitivity; tuberculin sensitive tissues. J. Exper. Med., 64:339, 1936.
225. Monchenberg, J.: Die Erkrankungen des [illegible] Spezifischen Muskelsystems. Henke-Lubarsch, Hdbch. d. spez. path. [illegible] n, 1924, p. 290.
226. More, R. H.; McMillan, G. C., and Duff, [illegible] of sulfonamide allergy in man. Am. J. Path., 22:703, 1946.
227. Morgulis, S., and Jacobi, H. P.: Perspective of biochemical defects in muscle in vitamin E deficiency. Quart. Bull. Northwestern Univ. M. School., 20:92, 1946.
228. Moritz, A. R., and Morley, J. D.: Shwartzman phenomenon in the knee joints of rabbits. Proc. Soc. Exper. Biol. & Med., 29:321, 1931.
229. Nagy, G.: Question of dysovaric purpura and roentgen castration in chronic hemorrhagic purpura. Ztschr. f. klin. Med., 102:284, 1925.
230. Neuberger, K. T.; Geever, E. F., and Rutledge, E. K.: Rheumatic pneumonia. Arch. Path., 37:1, 1944.
231. Odel, H. M., and Horton, B. T.: Angina pectoris; manifestation of thiocyanate sensitivity treated with histamine; report of three cases. Proc. Staff Meet., Mayo Clin., 18:279, 1943.
232. Old, J. W., and Russell, W. O.: Congenital heart disease with necrotizing arteritis (periarteritis nodosa) limited to the pulmonary arteries; report of a case with necropsy. Am. J. Path., 23:903, 1947.
233. Ophuls, W.: Periarteritis acuta nodosa. Arch. Int. Med., 32:870, 1923.
234. Opie, E. L.: Pathogenesis of the specific inflammatory reaction of immunized animals (Arthus phenomena). J. Immunol., 9:259, 1924.
235. Opie, E. L.: Inflammatory reaction of the immune animal to antigen (Arthus phenomenon) and its relation to antibodies. J. Immunol., 9:231, 1924.
236. Opie, E. L.: Desensitization to local action of antigen (Arthus phenomenon). J. Immunol., 9:247, 1924.
237. Orzechowski, K.: Disseminierte chronische Myositis und Lupus erythematosus. Arch. f. Dermat. u. Syph., 137:369, 1921.
238. Osgood, E. E., and Hunter, W. C.: Plasma cell leukemia. Folia haemat., 52:369, 1934.
239. Osler, W.: On the visceral complications of erythema exudativum multiforme. Am. J. M. Sc., 110:629, 1895.
240. Osler, W.: The visceral lesions of the erythema group. Brit. J. Dermat., 12:227, 1900.
241. Osler, W.: On the visceral manifestations of the erythema group of skin diseases. Am. J. M. Sc., 127:1, 1904.
242. Osler, W.: The visceral lesions of purpura and allied conditions. Brit. M. J., 1:517, 1914.
243. Pappenheimer, A. M.: Muscular disorders associated with deficiency of vitamin E. Physiol. Rev., 23:37, 1943.
244. Pappenheimer, A. M., and Von Glahn, W. C.: Studies on the pathology of rheumatic fever. Am. J. Path., 3:583, 1927.
245. Peale, A. R.; Gildersleeve, N., and Lucchesi, P. F.: Periarteritis nodosa complicating scarlet fever. Am. J. Dis. Child., 72:310, 1946.

246. Pernet, G.: Le lupus erythemateux aigu d'emblee. These de Paris, 1908.
247. Pollak, A. D.: Visceral and vascular lesions in scleroderma. Arch. Path., 29:859, 1940.
248. Race, R. R.: "Incomplete" antibody in human serum. Nature. London, 153:771, 1944.
249. Rackeman, F. W.: Clinical Allergy. New York: The MacMillan Co., 1931.
250. Rackeman, F. M., and Green, J. L.: Periarteritis nodosa and asthma. Tr. A. Am. Physicians, 54:112, 1939.
251. Rakow, H. L., and Taylor, J. S.: Acute disseminated lupus erythematosus, without cutaneous manifestations and with heretofore undescribed pulmonary lesions. Arch. Int. Med., 70:88, 1942.
252. Ratner, B.: Placental transmission of alimentary anaphylaxis. Proc. Soc. Exper. Biol. & Med., 30:88, 1932.
253. Ratner, B.: Allergy, Anaphylaxis, and Immunotherapy. Baltimore: Williams and Wilkins Co., 1943.
254. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Transmission of protein hypersensitiveness from mother to offspring; passive sensitization in utero. J. Immunol., 14:291, 1927.
255. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Transmission of protein hypersensitiveness from mother to offspring; active sensitization in utero. J. Immunol., 14:303, 1927.
256. Reifenstein, E. C.: Reifenstein, E. C., Jr., and Reifenstein, G. H.: A variable symptom complex of undetermined etiology with fatal termination including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sacks), fever of unknown origin (Christian), and diffuse peripheral vascular disease (Bachr and others). Arch. Int. Med., 63:553, 1939.
257. Reinman, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and periarteritis nodosa. J.A.M.A., 122:274, 1943.
258. Rice, D. A., and Scott, J. W.: Eosinophilia with transient lung infiltration (Loffler's syndrome). Canad. M. A. J., 57:286, 1947.
259. Rich, A. R.: The role of hypersensitivity in periarteritis nodosa. Bull. Johns Hopkins Hosp., 71:123, 1942.
260. Rich, A. R.: Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. Bull. Johns Hopkins Hosp., 71:375, 1942.
261. Rich, A. R.: Hypersensitivity to iodine as a cause of periarteritis nodosa. Bull. Johns Hopkins Hosp., 77:43, 1945.
262. Rich, A. R.: Hypersensitivity in disease, with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus, and rheumatoid arthritis. Harvey Lecture, 1946.
263. Rich, A. R.: Inflammation in resistance to infection. Arch. Path., 22:228, 1936.
264. Rich, A. R.: Acute splenic tumor produced by non-bacterial antigens. Proc. Soc. Exper. Biol. & Med., 32:1349, 1935.
265. Rich, A. R.: Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. Another case associated with sulfonamide reaction. Bull. Johns Hopkins Hosp., 71:375, 1942.
266. Rich, A. R., and Follis, R. H., Jr.: Studies on the site of sensitivity in the Arthus phenomena. Bull. Johns Hopkins Hosp., 66:106, 1940.
267. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins Hosp., 77:65, 1943.
268. Rich, A. R., and Gregory, J. E.: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Bull. Johns Hopkins Hosp., 73:239, 1943.
269. Rich, A. R., and Gregory, J. E.: Experimental anaphylactic lesions of the coronary arteries of the "sclerotic" type, commonly associated with rheumatic fever and disseminated lupus erythematosus. Bull. Johns Hopkins Hosp., 81:312, 1947.
270. Rich, A. R., and Gregory, J. E.: On the anaphylactic nature of rheumatic pneumonitis. Bull. Johns Hopkins Hosp., 73:465, 1943.
271. Rich, A. R., and Lewis, M. R.: The nature of allergy in tuberculosis as revealed by tissue culture studies. Bull. Johns Hopkins Hosp., 50:115, 1932.
272. Rich, A. R., and Lewis, M. R.: The mechanism of allergy in tuberculosis. Proc. Soc. Exper. Biol. & Med., 25:596, 1938.
273. Rittwagen, M.; Romano, F. J., and Soigals, M. P.: Incidence of allergy in children with rheumatic fever. Arch. Pediat., 63:639, 1946.
274. Roessle, R.: Die gewöhnlichen Ausserungen der Allergie. Wien. klin. Wchnschr., 45:609, 1932.
275. Roger, H., and Paillas, J.: Les complications encéphalique de la maladie sérique. Paris Med., 101:230, 1936.
276. Rose, E., and Goldberg, L. C.: Visceral lesions of acute disseminated lupus erythematosus. M. Clin. North America, 19:333, 1935.
277. Rose, E., and Pillsbury, D. M.: Acute disseminated lupus erythematosus—a systemic disease. Ann. Int. Med., 12:951, 1939.
278. Rost, G. A.: Lupus erythematosus als allergischhyperergische systemerkrankung. Arch. Dermat. u. Syph., Berlin, 186:259, 1947.
279. Rushmore, S.: Purpura complicating pregnancy. Am. J. Obst. & Gynec., 10:553, 1925.
280. Sanarelli, G.: Experimental cholera. Ann. de l'Inst. Pasteur, 38:11, 1924.
281. Sanarelli, G.: Hemorrhagic allergies (Sanarelli-Shwartzman phenomenon) in human and experimental pathology. Schweiz. med. Wchnschr., 65:95, 1935.
282. Sato, Y.: Über die spezifischen Organveränderungen der Kaninchen bei wiederholter, parenteraler Eiweisszufuhr. Trans. Soc. Path. Jap., 24:293, 1934.
283. Scherago, M.: Bacterial allergy. Ann. Allergy. 5:1, 1947.
284. Schonholzer, G.: Die Bindung von Prontosil und die Bluteiweiskorper. Klin. Wchnschr., 19:790, 1940.
285. Schuermann, B.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis). Arch. f. Dermat., 178:414, 1939.
286. Schwentker, F. F., and Comploier, F. C.: Production of kidney antibodies by infection of homologous kidney plus bacterial toxins. J. Exper. Med., 70:223, 1939.
287. Seegal, B. C., and Loeb, E. N.: Effect of anti-placenta serum on development of fetus in pregnant rat. Proc. Soc. Exper. Biol. & Med., 45:248, 1940.
288. Selye, H., and Pentz, E. I.: Pathogenetical correlations between periarteritis nodosa, renal hypertension, and rheumatic lesions. Canad. M. A. J., 49:264, 1943.
289. Senear, F.E., and Usher, B.: An unusual type of pemphigus, combining features of lupus erythematosus and pemphigus. Arch. Dermat. & Syph., 27:498, 1931.

290. Shookhoff, C., and Lieberman, D. L.: Hypersensitiveness to acetyl salicylic acid expressed by angina pectoris syndrome with and without urticaria. J. Allergy, 4:506, 1933.
291. Shute, E. V.; Vogelsang, A. B.; Skelton, F. R., and Shute, W. E.: The influence of vitamin E on vascular disease. Surg., Gynec. & Obst., 86:1, 1948.
292. Shwartzman, G.: Studies on Bacillus typhosus toxic substances phenomenon of local skin reactivity to B. typhosus culture filtrate. J. Exper. Med., 48:247, 1928.
293. Shwartzman, G.: Phenomenon of Local Tissue Reactivity. New York: Paul B. Hoeber, 1937.
294. Shwartzman, G.: Concerning specificity and nature of phenomenon of local skin reactivity to various bacterial filtrates. J. Exper. Med., 51:571, 1930.
295. Shwartzman, G.: Phenomenon of local skin reactivity to bacterial filtrates: elicitation of local reactivity by way of vascular system. J. Exper. Med., 62:621, 1935.
296. Shwartzman, G.: New method for demonstration of antigen-antibody combination. Science, 76:127, 1932.
296a Smadel, J. E., and Swift, H. F.: Experimental nephritis in rats induced by injection of anti-kidney serum; chronic nephritis of insidious development following apparent recovery from acute nephrotoxic nephritis. J. Exper. Med., 74:345, 1941.
297. Smith, C. E.: Menstrual purpura. New Orleans M. & S. J., 90:214, 1937.
298. Smith, C. C., and Zeek, P. M.: Studies on periarteritis nodosa. II. The role of various factors in the etiology of periarteritis nodosa in experimental animals. Am. J. Path., 23:147, 1947.
299. Smith, C. C.; Zeek, P. M., and McGuire, J.: Periarteritis nodosa in experimental hypertensive rats and dogs. Am. J. Path., 20:721, 1944.
300. Smoot, R. H.: Sulfonamide death with cerebral vascular necrosis and leukocytosis. Jefferson Hillman Hosp. Bull., 1:65, 1947.
301. Stickney, J. M., and Keith, N. M.: Renal involvement in disseminated lupus erythematosus. Arch. Int. Med., 66:643, 1940.
302. Swift, H. F.: Rheumatic fever. J.A.M.A., 92:2071, 1929.
303. Szepsenwol, J., and Witebsky, E.: Recherche de l'antigéne "Forsman" dans l'oeuf et dans certaines regions de l'embryon de poulet. Comp. rend. Soc. de Biol., 115:1019, 1934.
304. Taussig, L.: The Senear-Usher syndrome: A variety of lupus erythematosus. Arch. Dermat. & Syph., 27:498, 1933.
305. Taussig, A. E., and Somogyi, M.: Hyperglobulinemia in granuloma inguinale. J. Lab. & Clin. Med., 25:1070, 1940.
306. Towle, H. P.: Dermatomyositis. Arch. Dermat. & Syph., 34:298, 1936.
307. Treffers, H. P.; Heidelberger, M., and Freund, J.: Antiproteins in horse sera. IV. Antibodies to rabbit serum and their interaction with antigen. J. Exper. Med., 86:95, 1947.
308. Tremaine, M. J.: Subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis: A report of two fatal cases. New England J. Med., 211:754, 1934.
309. Tschamer, F.: Ein Weiterer Beitrag zur Kenntnis der Periarteritis nodosa. Frank. Zeitschr., 23:344, 1920.
310. Turner, J. C.: Dermatomyositis: A study of three cases. New England J. Med., 216:158, 1937.
311. Tyler, A.: Anaphylactic properties of photo-oxidized rabbit antisera (vs. sheep erythrocytes and pneumonia) and horse antiserum (vs. diptherial toxin) containing "univalent" antibodies. J. Immunol., 51:329, 1945.
312. Tyler, A.: Conversion of agglutinins and precipitins into "univalent" (non-agglutinating or nonprecipitating) antibodies by photodynamic irradiation of rabbit antisera vs. pneumococci, sheep red cells and sea urchin sperm. J. Immunol., 51:157, 1945.
313. Urbach, E.: Endogenous allergy. Arch. Dermat. & Syph., 45:697, 1942.
314. Urbach, E., and Shay, H.: Severe light hypersensitiveness cured by cholecystectomy. Ann. Allergy, 3:124, 1945.
315. Van der Sar, A.: Pulmonary ascariasis: its relationship to the eosinophil lung and Löffler's syndrome. Am. Rev. Tuberc., 53:440, 1946.
316. Vaubel, E.: Die Eiweissüberempfindlichkeit (Gewebshypercrgie) des Bindesgewebes. Ziegler's Beitr., 89:374, 1932.
317. Vaughn, W. T., and Hawks, E. K.: Angioneurotic edema with some unusual manifestations. J. Allergy, 2:125, 1931.
318. Verse, M.: Periarteritis nodosa and arteritis syphilotica cerebralis. Zeigler's Beitr., 40:409, 1907.
319. Volhard, F., and Fahr., K. T.: Die Brightische Nierenkrankheit. Berlin: Julius Springer, 1914.
320. Von Glahn, W. C., and Pappenheimer, A. M.: Specific lesions of peripheral blood vessels in rheumatism. Am. J. Path., 2:235, 1926.
321. von Meyenburg, H.: Das Eosinophile Lungeninfiltrate pathologische Anatomie und Pathogenese. Schweiz. med. Wchnschr., 72:809, 1942.
322. von Rokitanski, G.: Über einige der wichtigsten Erkrankungen der Arterien. Denkschr. d. k. Akad. d. Wissensch., 4:49, 1852.
323. Wadsworth, G. H., and Brown, G. H.: Serum reaction complicated by acute carditis. J. Ped., 17:80, 1940.
324. Wanderer, E.: Dermatomyositis. Zentralbl. f. Haut- u. Geschlechtskr., 53:145, 1936.
325. Watjen: Ein besondere Fall Rheumatische Myokarditis. Verh. d. deutch. path., Gesellschft., 18:223, 1921.
326. Watson, C. J.; Schultz, A. L., and Wikoff, H. M.: Purpura following estrogen therapy, with particular reference to hypersensitivity to (diethyl) stilbesterol and with a note on the possible relationship of purpura to endogenous estrogens. J. Lab. & Clin. Med., 32:606, 1947.
327. Wedum, A. G.: Immunological specificity of sulfonamide azoproteins. J. Infect. Dis., 70:173, 1942.
328. Wedum, A. G., and Wedum, B. G.: Serum precipitation reaction in rheumatic fever and in other conditions. Proc. Soc. Exper. Biol. & Med., 61:432, 1946.
329. Wiener, A. S.: New test (blocking test) for Rh sensitization. Proc. Soc. Exper. Biol. & Med., 56:173, 1944.
330. Wiener, A. S., and Karow, H. E.: Diagrammatic representation of the human blood group reactions. J. Immunol., 49:41, 1944.
331. Wilcox, H. B., Jr., and Andrus, E. C.: Anaphylaxis in isolated heart. J. Exper. Med., 67:169, 1938.
332. Williams, E. B., Jr., and Walker, W. H.: Löffler's syndrome: report of a case with a brief review of the literature. J. Nat. M. Assn., 39:211, 1947.

333. Wilmer, H. A.: Two cases of periarteritis nodosa occurring in the first month of life. Bull. Johns Hopkins Hosp., 77:275, 1945.
334. Wilson, C., and Byron, F. B.: Vicious circle in chronic Bright's disease. Experimental evidence from hypertensive rat. Quart. J. Med., 10:65, 1941.
335. Wilson, K. S., and Alexander, H. L.: Relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. J. Lab. & Clin. Med., 30:195, 1945.
336. Winternitz, M. C.; Mylon, E.; Waters, L. L., and Katzenstein, R.: Studies on relation of kidney to cardiovascular disease. Yale J. Biol. & Med., 12:623, 1940.
337. Wittich, F. W.: Active anaphylaxis in chick embryo; preliminary report. J. Allergy, 12:523, 1941.
338. Wittich, F. W.: Spontaneous allergy—atopy in lower animal seasonal hay fever (fall type) in dog. J. Allergy, 12:247, 1941.
339. Witts, L. J.: A case of dermatomyositis. Brit. J. Dermat., 48:509, 1936.
340. Wolbach, S. B.: Studies on rocky mountain spotted fever. J. Med. Research, 41:1, 1919.
341. Wolbach, S. B.; Todd, J. L., and Palfrey, F. W.: The etiology and pathology of typhus, being the main report of the Typhus Research Commission of the League of the Red Cross. Cambridge: Harvard University Press, 1922.
342. Yamada, K. I.: Effect of visible light on biologic reaction of eclamptic blood serum and eclamptic placenta. Jap. J. Obst. & Gynec., 23:141, 1940.
343. Zeek, P. M.; Smith, C. C., and Weeter, J. C.: Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and of hypersensitivity. Am. J. Path., 24:889, 1948.
344. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: Immunity. Ed. 5, pp. 384. New York: Macmillan Co., 1939.
345 Zondek, B., and Bromberg, Y. M.: Endocrine allergy. I. Allergic sensitivity to endogenous hormones. J. Allergy, 16:1, 1945.

The Marshfield Clinic

CORRECTIONS

PROGRESS IN ALLERGY: Physical Allergy in Dermatology, Stephan Epstein, M.D., F.A.C.A., Annals of Allergy, 6:617-623 (September-October), 1948. Tables I, II and III (pages 618-619) should read as follows:

TABLE I. HISTAMINE CONTENT OF SKIN AND BLOOD

Histamine content of skin		*Histamine content of blood*	
Author	γ (gamma)/gm.	Author	γ (gamma)/gm.
Nilzén	5 – 24	Rose & Browne	0.023 – 0.08
Pellerat & Murat	16 – 24	Nilzén	0.045 – 0.084

1 γ (gamma) = 0.001 mgm.

TABLE II. HISTAMINE CONTENT OF SKIN IN NORMAL INDIVIDUALS AFTER MECHANICAL STIMULATION

	Average values from Nilzén	
Time	*Normal skin*	*Wheal*
	γ (gamma)/gm.	γ (gamma)/gm.
2 min.	7.6	6.3
10 min.	11.5	6.2
25 min.	8.4	5.2
50 min.	11.6	11.3

TABLE III. HISTAMINE CONTENT OF SKIN IN DERMOGRAPHIA AFTER MECHANICAL STIMULATION

Time	*Normal skin*	*Wheal*
	γ (gamma)/gm.	γ (gamma)/gm.
2 min.	13.	10.3
5 min.	10.6	6.3
10 min.	16.	8.7

* * *

A Clinical Evaluation of Orthoxine in the Treatment of Allergic Diseases, F. W. Wittich, M.D., F.A.C.A., Annals of Allergy, 6:664-666, (November-December), 1948.

The first sentence of the summary should read as follows: Orthoxine has advantages over ephedrine in that it is not affected by digestion and may be given orally.

News Items

LOS ANGELES SOCIETY OF ALLERGY

At the annual meeting of the Los Angeles Society of Allergy (a Section of the Los Angeles County Medical Association), the following officers were elected for 1949: Hyman Miller, M.D., President; Frank G. Crandall, Jr., M.D., Vice President; M. Coleman Harris, M.D., Secretary-Treasurer. These officers were installed at the January meeting of the Society.

ARGENTINE SOCIETY OF ALLERGY

The Directive Council of the Argentine Society of Allergy was changed December 30, 1948, and the following members have been elected: Dr. Miguel Agustin Solari, President; Dr. Jose Martorelli, Vice President; Dr. Alois E. Bachmann, Secretary; Dr. Rodolfo Monti, Sub-secretary; Dr. David M. Xanalda, Treasurer; Dr. Ladislao Naon, Sub-treasurer; Drs. Manuel Estiu, Jose F. Dumm, Vicente Galvagno, Ozcar Zarate, and Osvaldo Crivelli, Auxiliaries; and Drs. Mariano R. Castex, Caupolican Castilla, and Guido Ruiz Moreno, Advisers.

CONNECTICUT ALLERGY SOCIETY

The fall meeting of the Connecticut Allergy Society was held at the Hotel Bond, Hartford, October 27, 1948, with S. W. Jennes, M.D., Waterbury, presiding. An extremely interesting program including a round table discussion on "Asthma" was arranged by Drs. A. F. Roche and Vincent Cenci of Hartford. A spirited discussion of the various phases of the subject took place. Plans were initiated for the next meeting of the Society which will be held in the spring in conjunction with the annual meeting of the Connecticut State Medical Society.

BRAZILIAN ALLERGY SOCIETY

The Brazilian Allergy Society sponsored an Instructional Course in Allergy at Rio de Janeiro November 16 to 26, 1948. These lectures will be published in a medical review. It is very interesting to learn that about 160 physicians registered for this first course in allergy, and we congratulate the Brazilian Allergy Society on its educational program.

The Directory of the Brazilian Allergy Society for 1949 is as follows: Dr. Nelson Passarelli, President; Dr. Eleutherio Brum Negreiros, Vice President; Dr. Paulo Dias da Costa, re-elected First Secretary; Dr. Jose Eduardo de Abreu, Second Secretary; Dr. Affonso de Negreiros Sayao Lobato, Treasurer; Dr. Percy Pereira dos Santos, Librarian; and Drs. Edgard Luz, Tamara Rubinstein, and Haroldo Cardoso de Castro, Advisory Board.

THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

The International Association of Allergists has been officially notified by Professor J. Maisin, President of the Executive Committee, Permanent Bureau for the Coordination of International Congresses of Medical Sciences, a joint activity of the United Nations Educational, Scientific and Cultural Organizations and of the World Health Organization, that it has been accepted as a member of this Bureau. The IAA has been invited to participate in the work of a conference of this Bureau which will be held in Brussels from April 4 to April 9, 1949, under the auspices of UNESCO and the OMS. Professor A. Grumbach, Associate Professor, Preventive Medicine and Bacteriology, Zurich University, a member of the Executive Committee of the International Association of Allergists and one of the editors of the *International Archives of Allergy and Applied Immunology*, has been appointed by the Executive Committee of the International Association of Allergists as the official delegate to this conference. An invitation has been received to hold the first Congress at Zurich.

PENNSYLVANIA ALLERGY ASSOCIATION

The Central Pennsylvania Allergy Society will hereafter be known as the Pennsylvania Allergy Association. By an overwhelming vote of approval, it was deemed advisable to change the name because many members of the association are from all parts of the state. While many members are also members of either the Philadelphia Allergy Society or the Pittsburgh Allergy Society, it is important that it be known that these three groups are distinct and separate organizations.

The spring meeting of the association will be held in Allentown on the first Wednesday in April, with Dr. Alexander Peters as chairman. The fall meeting in 1949 will be held in Pottsville, with Dr. Joseph Ricchuiti as chairman.

The following members were chosen as officers for the year 1949: Dr. Harvey Simmons, Harrisburg, President; Dr. Alexander Peters, Allentown, Vice President; Dr. Ralph M. Mulligan, Reading, Secretary-Treasurer.

The following men were elected to the Board of Regents: Dr. Archibald Judd Hamburg, and Dr. Stephen Lockey, Lancaster, *Chairman* (three years); Dr. Luther King, Meadville, and Dr. J. V. Foster, Jr., Harrisburg (two years); Dr. Alexander Peters, Allentown, and Dr. Warren Brubaker, Annville (one year). The president and the secretary-treasurer automatically become members of this body.

THE AMERICAN COLLEGE OF PHYSICIANS OFFERS POSTGRADUATE COURSE

The American College of Physicians has among its activities the organization and conduct of numerous, short intensive, advanced, postgraduate courses in Internal Medicine and its allied branches. On the schedule for the first half of 1949, it offers a course in "Diseases Caused by Immune Mechanisms," under the direction of Dr. Leo H. Criep, Associate Professor of Medicine at the University of Pittsburgh School of Medicine.

The course will cover the immunology, pharmacology, physiology, and clinical phases of diseases due to immune mechanisms. It will cover the fundamental concept of immunity, including antigen, antibody formation—antigen antibody reactions, histamine, anaphylaxis, and atopy. The following conditions will be discussed: erythroblastosis fetalis—transfusion reactions; atopic disorders; asthma, nasal allergy, atopic dermatosis, pediatric allergy, and serum disease pattern; allergy due to chemicals and drugs; cross sensitization; contact dermatitis and drug allergy; allergy due to infectious agents; bacteria and viruses—brucellosis, tuberculosis, rheumatic fever, scarlet fever, acute glomerular nephritis; periarteritis nodosa; diseases of doubtful etiology; rheumatoid arthritis and collagen diseases.

This course will be organized and directed as a graduate course for internists and allergists and should appeal also to the pediatrician, rhinologist, and dermatologist. In view of the fact that several medical groups will be holding meetings in Atlantic City at this time—April 28-May 1, inclusive, 1949—the course, instead of being given at the University of Pittsburgh School of Medicine, will be given at Haddon Hall Hotel, Atlantic City, New Jersey. The class will be limited to a group of fifty. Fee to members of the American College of Physicians, $30; non-members, $60.

For full information about details of the course, address the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

GENERAL NEWS

Dr. Carl D. Marsh and Dr. David W. Goltman announce their association in the practice of Allergy and the removal of their offices to 36 South Bellevue, Memphis, Tennessee.

* * *

Dr. Joseph F. Griggs of Claremont, California, presented a paper on "Bacterial Allergy in Chronic Brucellosis" at the Second Inter-American Congress on Brucellosis held in Buenos Aires, November 22. The Congress was sponsored by the Pan

American Sanitary Bureau, Washington, D. C. Dr. Griggs' paper will appear in a forthcoming issue of the ANNALS OF ALLERGY.

* * *

We are pleased to announce the addition of Professor Piero Sangiorgi of Milan, Italy, to the Editorial Board of the *International Archives of Allergy and Applied Immunology,* the official publication of the International Association of Allergists, Inc. It is hoped that the first issue of this journal will appear early this spring. S. Karger, Basel, Switzerland, are the publishers of the *Archives.* Subscriptions may be made through Interscience Publishers, Inc., 214 4th Avenue, New York 3, N. Y. The subscription price is $10.00 a year.

* * *

PROGRESS IN THE SCIENCE OF ALLERGY. Fortschritte der Allergielehre Vol. II. Edited by Paul Kallós, M.D., Helsingborg, Sweden. New York and Basel: S. Karger, Medical Publisher. 352 pages. Illustrated.

As in Volume I, the principle of adhering to independent contributions, covering some special domain in research or clinic, has been continued. Equal consideration is given to theoretical and practical problems.

Following a comprehensive introductory review (in German), the following chapters are presented: *Immunochemistry* by Dr. Elvin A. Kabat; *Allergic Diseases in Animals* by Dr. Fred W. Wittich; *Indications for Bronchoscopic Therapy in Asthma* and *An Etiological Survey of Chronic Urticaria* by Dr. George L. Waldbott; *Present Status of Aerosol Therapy of the Lungs and Bronchi* by Dr. Harold A. Abramson; *The Diagnosis and Treatment of Allergies of the Nose and Paranasal Sinuses* and *Small Dosage Dust and Pollen Therapy* by Dr. French K. Hansel; *Allergy in the Middle Ear* by Dr. Hjalmar Koch; *Allergy in Diseases of the Skin* by Dr. Holger Haxthausen; *Allergy to Human Dander in Infantile Eczema* by Dr. Frank A. Simon; *Allergy of the Nervous System with Especial Reference to Migraine* by Dr. Foster Kennedy with an Addendum on *The Basis for Allergy in Diseases of the Nervous System* by Dr. Robert A. Cooke; *Allergy as a Cause or a Mechanism in Disseminated Sclerosis* by Dr. Lewis Stevenson; *Pharmacology of the Antihistaminics* (in German) by Dr. R. Meier and Dr. K. Bucher; and *The Clinical Application of the Histamine Antagonists* (in German) by Paul Kallós and Dr. Liselotte Kallós-Deffner.

Each subject is compactly reviewed in a masterful way by authorities in their respective fields.

* * *

NECROLOGY

As the ANNALS goes to press, we regret very much to report the deaths of the following Active Fellows of the College: Dr. George C. Anglin, Toronto 5, Ontario, Canada; Dr. Voyle M. James, Hollywood, California; Dr. Philip J. Jordan, San Jose, California, and Dr. William A. Mowry, Madison, Wisconsin. Condolences have been sent to the bereaved families and obituaries will appear in the March-April issue.

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BOOK REVIEWS

PSYCHODYNAMICS AND THE ALLERGIC PATIENT. By Harold A. Abramson, M.D., with a Panel Discussion. 81 pages. 7 figures. Price $2.50. St. Paul and Minneapolis: The Bruce Publishing Company. 1948.

This book, an official publication of The American College of Allergists, represents the first step in the co-ordination of organizational allergy and psychodynamics. The object is to focus on the importance of emotional factors in the routine therapy of the allergic patient by both the allergist and the general practitioner.

Besides two articles by the author, it records the first panel discussion on the role of psychodynamics and the allergic patient, arranged by allergists under the auspices of The American College of Allergists at its third annual meeting held in Atlantic City, New Jersey, June 8, 1947.

Among the invited psychiatrists attending the meeting were Drs. O. Spurgeon English, Frank Fremont-Smith, J. A. P. Millet, Sandor Rado, and Edward Weiss. By bringing together authorities in the field of psychiatry and authorities interested in the immunologic aspects of the problem involved in treating the allergic patient, it was possible to take this first step in the consideration of the co-ordination of the disciplines of applied immunology and of psychodynamics on the same program in a constructive way. It may be mentioned that the reviewer notes that a result of this Symposium is reflected in the greater interest developed in the subject of psychodynamics by allergists.

A chapter on the psychosomatic aspects of hay fever and asthma prior to 1900, by the author, is a chronologic history revealing that even in their relatively primitive therapy, our medical ancestors not only recognized the syndromes of hypersensitivity corresponding to what is now on an immunologic basis, but also stressed the relationship between the psyche and allergic diseases in no uncertain way. This chapter contains many suggestions for historical exploration in the field of psychodynamics in connection with allergic syndromes.

The author's article on "Psychodynamics and the Allergic Patient" brings forth convincing evidence of the inadequacy of the histamine theory of allergy and the importance of emotional factors. The author feels that it is necessary to be specific in characterizing motivation by specific psychomotive forces and, in other cases, neuromotive forces. The term "motive force" is not sufficiently specific to emphasize the primary role of the psyche which contains unmeasurable quantities. Various case records are given which classify allergic syndromes into those where immunologic factors are definitely always present and those where immunologic factors have not been proven.

The book is neatly bound in durable board, is of good paper stock and has clear illustrations. All students of allergy and psychiatry will be stimulated by this free discussion of controversial questions.

CLINICA MEDICA. Nino Marsiaj, M.D. 474 pages, 16 chapters, 39 illustrations. Published and edited in Buenos Aires: Bartolome U. Chiesino, Ameghino 838-Avellaneda, 1948. Price, $4.00.

For many years Dr. Marsiaj, a faculty member of the University of Puerto Alegre, has had in mind a book for the advanced student of medicine. The comprehensive treatment of various cases encountered in the practice of modern Brazilian medicine makes it of outstanding value. It contains chapters on intestinal amoebiasis, myasthenia gravis and several allergy-associated syndromes. Of particular interest to the allergists are the following chapters:

1. Loeffler's Syndrome, with illustrations and descriptions of procedures followed in recently attended cases,

2. Tropical Eosinophilia and its relation to Loeffler's Syndrome, with a comparative chart of symptoms, evolutions, and treatment of the two,
3. Horton's Syndrome, in which the author makes a critical study of Horton's theories and includes a clinical chart of cases treated under his supervision.

Another section of the book to be considered by the allergist is the chapter devoted to Allergic Toxemia, its diagnosis, and treatment.

This readable and modern book is well conceived and would be an invaluable addition to the library of the advanced medical student as well as to the practicing physician. The paper stock, print and illustrations are of good quality. The book is written in Spanish.

USE OF CEVITAMIC ACID IN THE SYMPTOMATIC AND CO-SEASONAL TREATMENT OF POLLINOSIS

(Continued from Page 70)

13. McDonald, F. M. and Johnson, H. H.: Ascorbic acid and arsphenamine dermatitis. Arch. Dermat. & Syph., 43:682, 1941.
14. Pijoan, N. and Lozner, E. L.: The physiological significance of Vitamin C in man. New England M. J., 231:14, 1944 (87 refrences).
15. Rudra, M. N.: Role of manganese in the biological significance of ascorbic acid. Nature, 153:743, 1944.
16. Ruskin, S. L.: Studies on parallel action of Vitamin C and calcium. Am. J. Dig. Dis., 5:408, 1938; Further contribution to comparative studies of physico-chemical properties of gluconate and cevitamate of calcium and vitamin C. Am. J. Dig. Dis., 5:676, 1938; Influence of Vitamin C on the anti-histamine action of various drugs. Arch. Otolaryngol., 36:853, 1942.
17. Steinbach, M. M. and Klein, S. J.: Effect of ascorbic acid on tolerance to tuberculin. Proc. Soc. Exper. Biol. & Med., 35:151, 1936.
18. Sulzberger, M. D. and Oser, B. L.: Influence of ascorbic acid of diet on sensitization of guinea pigs to neoarsphenamine. Proc. Soc. Exp. Biol. & Med. 32:716, 1935.
19. Walther, C.: Allergic pneumonia and Vitamin C. Ztschr. t. d. ges. exper. Med., 106:749, 1939.
20. Walzer, M.: A critical review of the recent literature on the dust atopen and Vitamin C. J. Allergy, 10:74, 1938.
21. Yoshikawa, K.: On the antiallergic effect of Vitamin C. Nagasaki Igakkai Zassi, 17:165, 1939.

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1. Levin, S. J., and Moss, S. S.: *Hydryllin in Asthma and Hay Fever, J. Michigan M. Soc. 47:869 (Aug.) 1948.*

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2. Brown, E. B., and Brown, F. W.: *The Use of a New Antihistaminic Combination [Hydryllin] in the Treatment of Allergic Disorders, New York State J. Med. 48:1465 (July 1) 1948.*

34 CASES

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3. *Report of the Committee on Therapy to the American Academy of Allergy, St. Louis, Dec. 15-17, 1947.*

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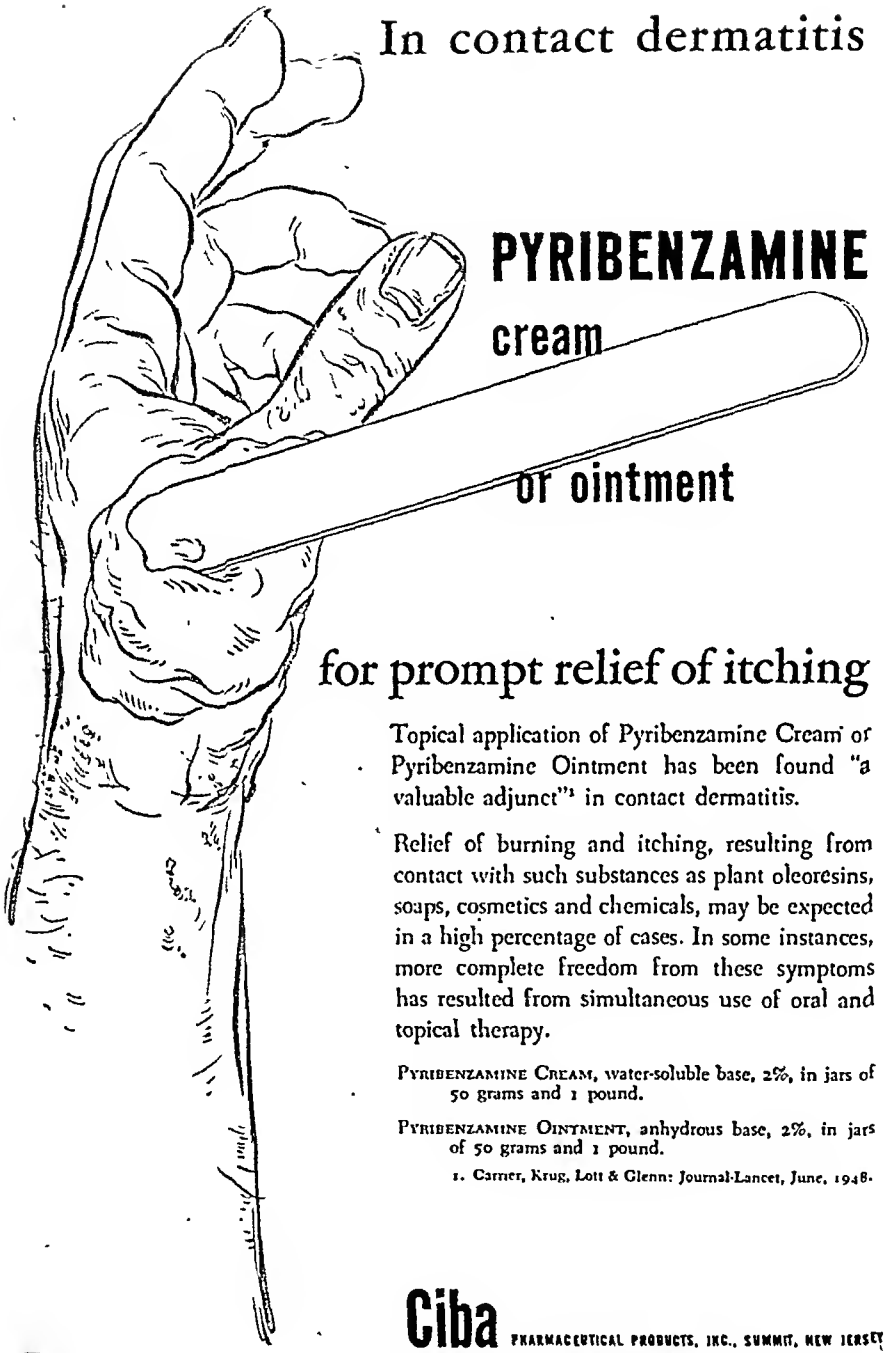

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1. Carmer, Krug, Lott & Glenn: Journal-Lancet, June, 1948.

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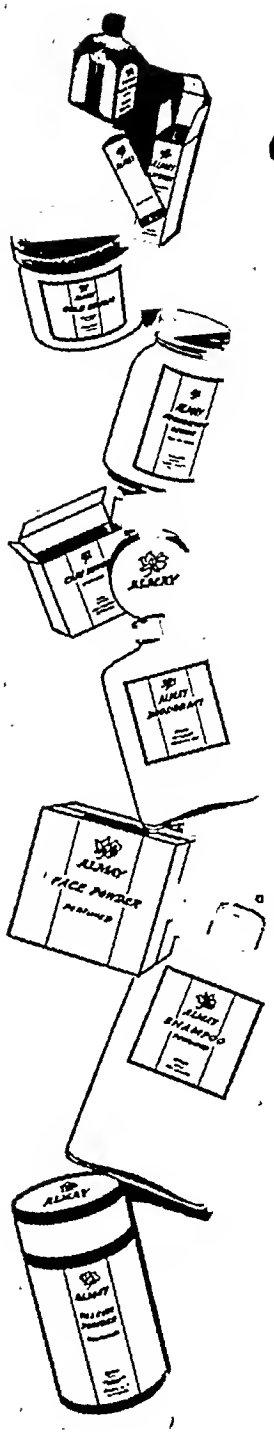

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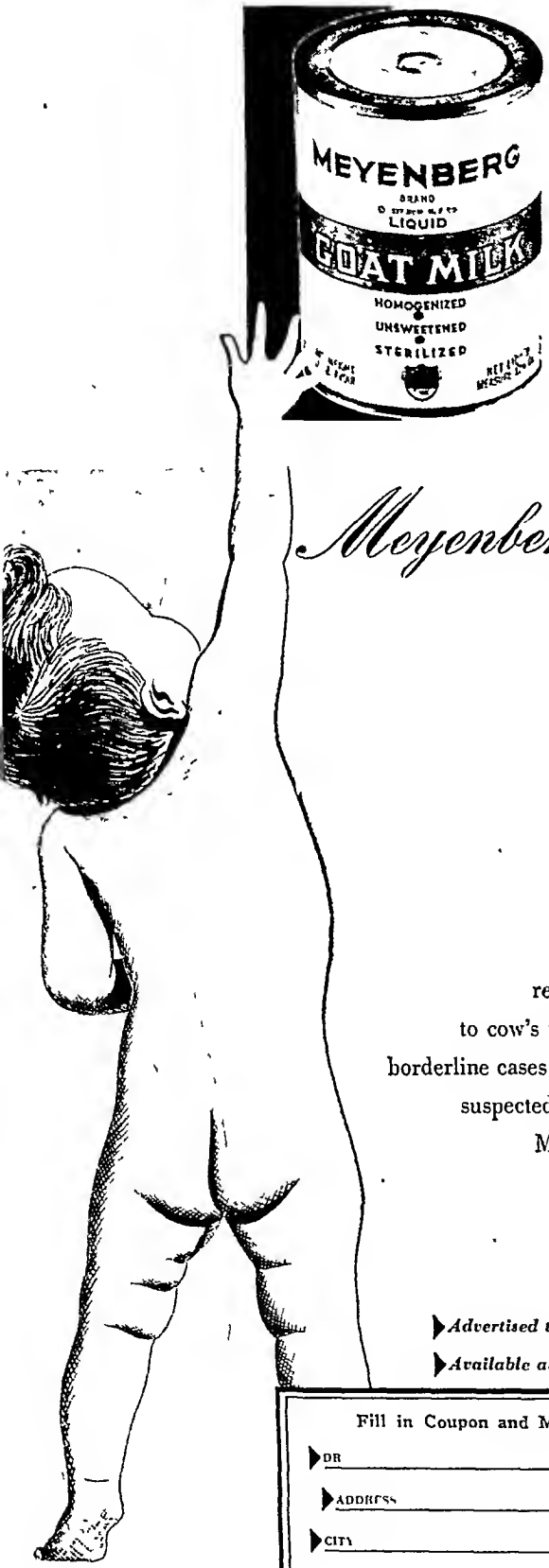

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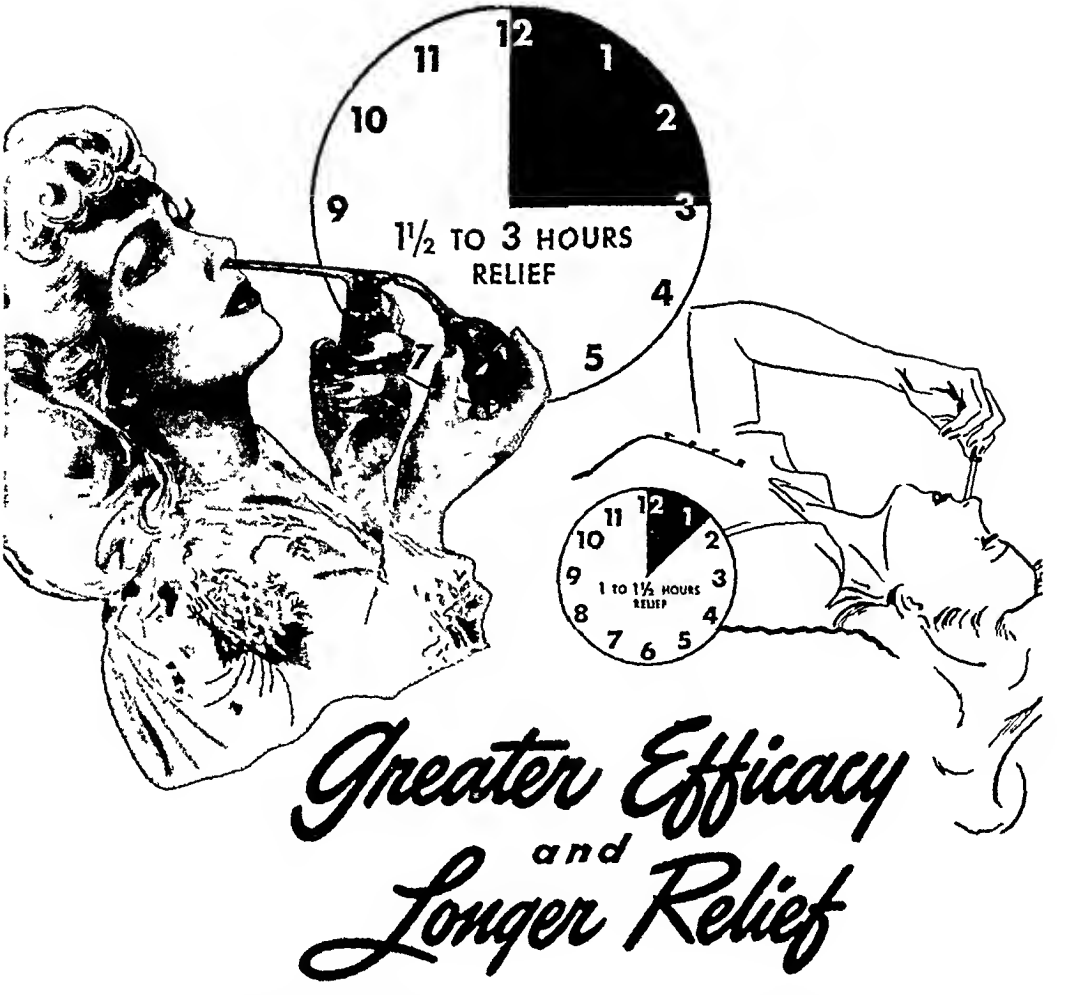

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1. PERSKY, H. A.: Penicillin-Vasoconstrictor Treatment of Post-Influenzal Rhinitis and Sequellae," Medical Record, November, 1947.

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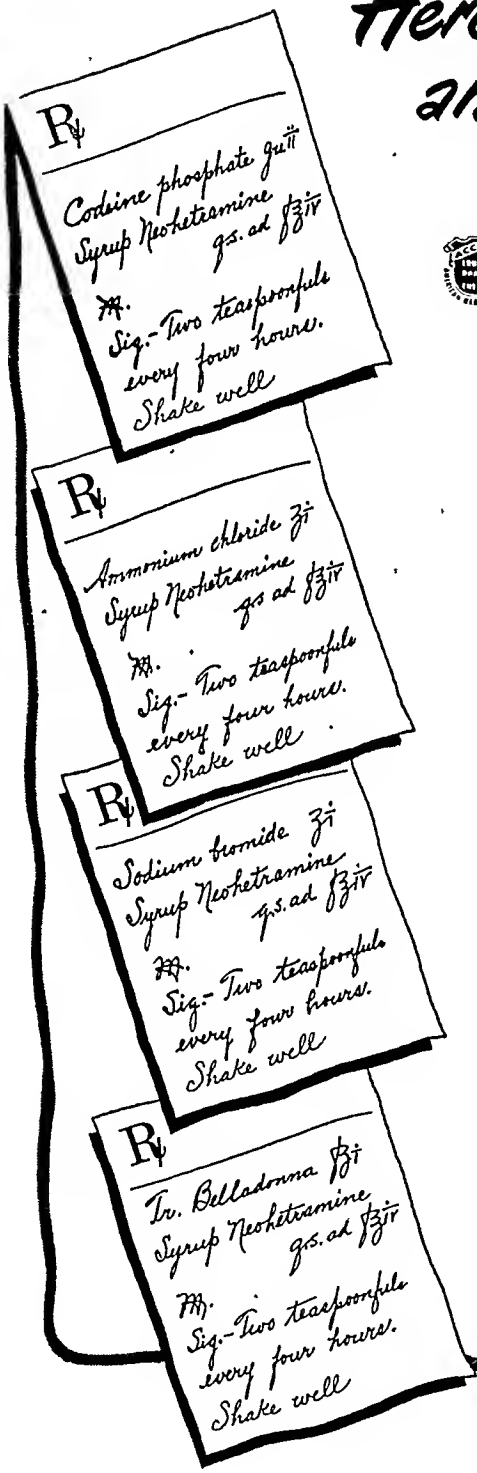

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1. Criep, Leo H., and Aaron, Theodore H., *Neohetramine: An Experimental and Clinical Evaluation in Allergic States*, The Journal of Allergy, Vol 19, No. 4, pp. 215-224, July, 1948.

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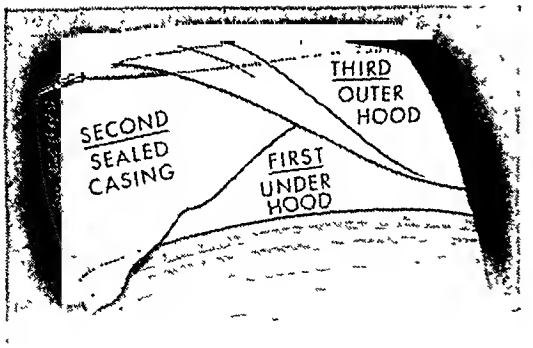

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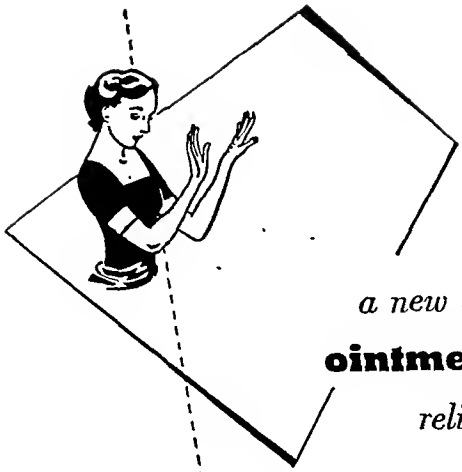

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See page 153 for review

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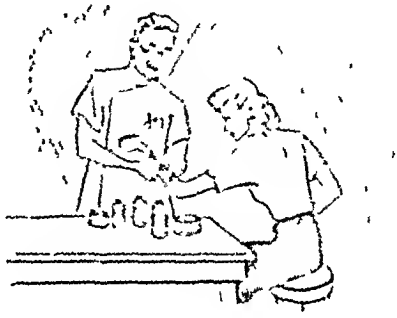
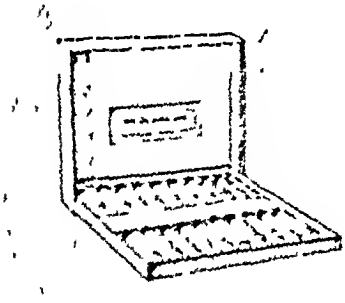
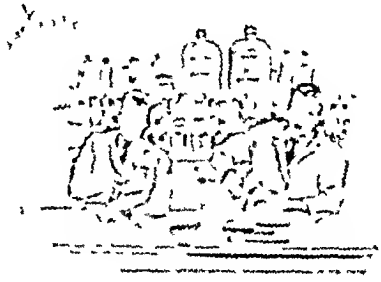




2) Secondary tests with constituents of products causing reaction, to trace offending agents. (In specific cases, on written request, we supply testing materials, gratis.)

3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)



4) Final check tests with modified formulae to make certain there is no reaction.

[illegible] Luzier are regularly available [illegible] They [illegible] Any of the [illegible] testing [illegible]

LUZIER'S, INC., MAKERS OF FINE COSMETICS . . KANSAS CITY 3, MO.